CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21698

STATISTICAL REVIEW(S)

MEMORANDUM OF STATISTICAL CONSULTATION

Medical Division: Gastrointestinal and Coagulant Drug Product (HFD-180)
Biometrics Division: Division of Biometrics II (HFD-715)

STATISTICAL KEY WORDS:
NDA #: 21-698
SERIAL NUMBER:
DATE RECEIVED BY CENTER: October 31, 2003
DRUG NAME: OTC Zantac 150 (ranitidine 150 mg) tablet
INDICATION: Prevention of heartburn
SPONSOR; Pfizer Consumer Healthcare
DOCUMENTS REVIEWED: Statistics Review and Evaluation for OTC Zantac 150mg dated 8/19/04
Statistics Review and Evaluation for OTC Zantac 75mg dated 8/12/97
Statistics Review and Evaluation for Pepcid AC 20mg dated 9/4/04
Statistics Review and Evaluation for OTC Zantac 150mg dated 8/19/04
Statistics Review and Evaluation for Axid AR 75mg dated 5/23/95
Statistics Review and Evaluation for Axid AR 75mg dated 10/29/97
Statistics Review and Evaluation for Tagamet HB 200mg dated 8/19/04
STATISTICAL REVIEWER: Milton C. Fan, Ph.D. (HFD-715)
STATISTICAL TEAM LEADER: Stella Grosser, Ph.D. (HFD-715)
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CLINICAL REVIEWER: Eric Brodsky, M.D. (HFD-180)
PROJECT MANGAGER: Diane Moore (HFD-180)

A. Background

Over-the-Counter (OTC) Zantac 75 (Ranitidine 75mg tablet) was approved in December 19, 1995 for relief of heartburn. OTC Zantac 75 was approved in June 8, 1998 for the prevention of heartburn.

In the current NDA, the sponsor seeks approval of the Over-the-Counter (OTC) use of Zantac 150 (Ranitidine Tablet 150 mg) for the prevention of heartburn

The sponsor has submitted three Phase III studies: (RAN3016, RAN3018 and RAN4006) supporting the prevention of heartburn.

These three studies had been statistically evaluated by this reviewer and had been documented in August 19, 20049 for comparing ranitidine 150mg versus placebo. In my review it stated "Two of the three clinical studies (RANA3016 and RANA4006) suggest that ranitidine 150mg was more effective than placebo for reducing severity of meal-induced heartburn when taken right before meal. In the other study (RAN3018), the ranitidine 150mg was not significantly better than placebo for the primary and most secondary efficacy parameters."

It also stated that for more clinical meaningful clinical endpoint, complete prevention, all of these three studies failed to show that ranitidine 150mg was statistically different from placebo. Treatment differences ranged from 2% to 3%. The detailed results of complete prevention are given in Attachment 1.

B. **Reviewer's Comments and Evaluation**

Per request from Dr. Korvick, acting medical division director, the results of complete prevention from statistical review and evaluation for all other OTC submissions for H_2-receptor antagonists (Zantac 75mg, Pepcid AC 20mg, Arix AR 75mg and Tagamet HB 200) are summarized .

The brief description for each OTC submission is given below.

For OTC Zantac 75mg, three studies (RANA3009, RANA3010, and RANA4005) had been conducted in support of the indication of prevention or reduction of meal-induced heartburn when taken 30-minute to one hour prior to a provocative meal. The statistical review and evaluation for this submission was done by Dr. Mushfiqur Rashid and was documented in August 12, 1997.

It was stated in the conclusion that the efficacy data in studies RANA3009 and RANA4005 indicated that Zantac 75mg was effective in the reduction of severity of heartburn symptoms in patients 18 years or older when administered 30 minutes (RANA4005) to one hour (RANA3009) prior to consuming food and beverages anticipated to provoke heartburn. This conclusion was drawn because of only one (RANA4010) of the three studies showed the Zantac 75mg was effective in the complete prevention.

The detailed results of complete prevention are given in Attachment 2.

For Tagamet HB 200, two studies (MD-01000 and MD-01001) had been conducted in support of the indication of prevention of meal-induced heartburn when taken just before or anytime up 30-minute prior to a provocative meal. The statistical review and evaluation for this submission was done by Dr. Mushfiqur Rashid and was documented in March 23, 1998.

It was stated in the conclusion that the efficacy data in studies MD-01000 and MD-01001 indicated that Tagamet 200 when administered prior to consuming food and beverages

anticipated to provoke heartburn, was more effective than placebo in preventing heartburn within three hours of the meal. Also the efficacy data in both studies indicated that Tagamet 200 was significantly more effective than placebo in reducing heartburn severity with three hours of administration. Although both studies showed that Tagamet 200 patients had a numerically higher duration of no heartburn than those of placebo, only one of the studies (MD-01001) shows a significant difference in favor of Tagamet 200.

The detailed results of complete prevention are given in Attachment 3.

For Axid AR 75mg, there were two submissions. For the first submission, two studies (WM-560 and WM-576) had been conducted in support of the indication of prevention of meal-induced heartburn. For study WM-560, patients were to received a single dose of the test drug 60 minutes prior to receive the standard provocative test meal, while for study WM-576, a single dose to the test drug was to be taken 30 minutes prior to receiving the standard provocative test meal. The statistical review and evaluation for this submission was done by Dr. A. J. Sankoh and was documented in May 23, 1995.

It was stated in the conclusion that the efficacy data supported the effectiveness of nizatidine 75mg dose in preventing/reducing heartburn when taken 30 or 60 minutes prior to meal-inducing (provoking) heartburn.

For the second submission, two studies (NZ-95-02 and NZ-95-03) had been conducted in support of the indication of prevention of heartburn, acid indigestion, and sour stomach related to foods and beverage when taken 0 to 15 minutes before eating or drinking. For both studies (NZ-95-02 and NZ-95-03) , patients were randomized to one of three treatment groups at both 15 minutes and immediately before the test meal; i.e., Axid 75mg at 15 minutes before the test meal and placebo immediately before the test meal, or placebo at 15 minutes before the test meal and Axid 75mg immediately before the test meal. The statistical review and evaluation for this submission was done by Dr. Mushfiqur Rashid and was documented in October 29, 1997.

It was stated in the conclusion that efficacy data in studies NZ-95-02 and NZ-95-03 indicated that Axid 75mg was significantly effective in the complete prevention of heartburn symptoms in patients 16 years or older when administered immediately (0-min) prior to consuming food and beverage anticipated to provoke heartburn. Regarding Axid 75mg taken 15 minutes before a meal provoking heartburn, the effectiveness results favoring Axid 75mg were not as convincing as those in favor of Axid 75mg taken immediately before the provoking meal.

The detailed results of complete prevention are given in Attachments 4 and 5.

For Pepcid AC 20mg, three studies (114, 117, and 128) had been conducted in support of the indication of prevention of meal-induced heartburn when taken —— prior to a provocative meal. The statistical review and evaluation for this submission was done by this reviewer and was documented in September 4, 2003.

It was stated in the conclusion that all three studies (114, 117 and 128) showed that famotidine 20 mg was superior to placebo in terms of peak heartburn severity during the 3 hours postmeal. Furthermore, study 117 showed that peak heartburn symptoms were statistically significantly less severe with famotidine 20mg than with famotidine 10mg. Study 128 also showed that famotidine 20mg was marginally significantly better than famotidine 10mg.

For proportion of patients reporting no heartburn during the 3 hours following the start of the meal, it was stated in the review that all three studies showed that there was a significantly greater percentage of patients with no heartburn in the famotidine 20mg group than the placebo group.

The detailed results of complete prevention are given in Attachment 6.

The summary of results of analysis of complete prevention of heartburn from statistical review and evaluation for all OTC submissions for H_2-receptor antagonists (Zantac 150mg, Zantac 75mg, Pepcid AC 20mg, Axid AR 75mg and Tagamet HB 200) are given below.

Summary of Complete Prevention for H_2-receptor Antagonists

		Test Drug		Placebo			2-sided
Drug	Study	N	(%)	N	(%)	Treatment Diff	p-value
Zantac 150 mg[a]	RAN3016	283	7%	283	5%	2%	0.306
	RAN3018	277	10%	270	7%	3%	0.328
	RAN4006	181	12%	188	9%	3%	0.428
Zantac 75mg[b]	RANA3009	141	13%	133	9%	4%	0.2446
	RANA3010	153	14%	156	10%	4%	0.1822
	RANA4005	137	16%	132	5%	11%	0.0058
Tagamet 200 HB[c]	MD-01000	172	29%	173	17%	12%	0.01
	MD-01001	182	24%	183	15%	9%	0.036
Axid AR 75mg	WM-560[d]	80	20%	147	3%	17%	<0.001
	WM-576[e]	101	15%	103	3%	12%	<0.001
	NZ-95-02[f]	202	22%	204	11%	11%	0.002
	NZ-95-02[g]	203	22%	204	11%	11%	0.004
	NZ-95-03[f]	184	19%	187	14%	5%	0.166
	NZ-95-03[g]	184	27%	187	14%	13%	0.001
Pepcid AC 20mg[h]	114	261	11%	262	4%	7%	0.004
	117	488	38%	249	19%	19%	<0.001
	128	531	41%	264	27%	14%	<0.001

[a] taken right before eating food or drinking beverage that causes heartburn
[b] taken 30 minutes to one hour prior to consuming heartburn provoking food and beverages.
[c] taken at the start of a provocative meal.
[d] taken 60 minutes prior to receiving the standard provocative test meal.
[e] taken 30 minutes prior to receiving the standard provocative test meal.
[f] taken 10 minutes before a test meal.
[g] taken immediately before a test meal.
[h] taken 10 minutes prior to provocative meal.

As seen from table above, all H_2-receptor Antagonists approved for prevention of heartburn had a least one positive study. For Zantac 150mg, all of three studies (RAN3016, RAN3018, and RAN4006) failed to show statistically significance from placebo for complete prevention. Treatment differences ranged from 2% to 3%, about 10% less than those from other H_2-receptor antagonists.

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Attachment 1: Summary of Complete Prevention of Heartburn for Zantac 150mg

Summary of Complete Prevention of Heartburn
Protocol RAN3016
Intent-to-Treat Population

Treatment Meal

Treatment	Complete Prevention	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	16/263 (6%)	0.442	
Ranitidine 150mg	20/283 (7%)	0.306	0.905
Placebo	15/283 (5%)		

Copied from Table 18.
P-values were calculated using Mantel-Haenszel test stratified by investigator.
Only subjects who reported not having heartburn symptoms at the start of the meal were included in the analysis.
Correction was made in Adjustment to Clinical Report

Summary of Complete Prevention of Heartburn
Protocol RAN3018
Intent-to-Treat Population

Treatment Meal

Treatment	Complete Prevention	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	24/275 (9%)	0.631	
Ranitidine 150mg	28/277 (10%)	0.328	0.519
Placebo	20/270 (7%)		

Copied from Table 17.
P-values were calculated using Mantel-Haenszel test stratified by investigator.
Only subjects who reported not having heartburn symptoms at the start of the meal were included in the analysis.

Summary of Complete Prevention of Heartburn
Protocol RAN4006
All Subjects Population

Treatment Meal

Treatment	Complete Prevention	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	20/177 (11%)	0.449	
Ranitidine 150mg	22/181 (12%)	0.428	0.885
Placebo	17/188 (9%)		

Copied from Table 18.
Correction was made in Adjustment to Clinical Report.
P-values were calculated using Mantel-Haenszel test stratified by investigator.
Only subjects who reported not having heartburn symptoms at the start of the meal were included in the analysis.

Copied from Statistical Review and Evaluation for OTC Zantac 150mg dated 8/19/04

Attachment 2: Summary of Complete Prevention of Heartburn for Zantac 75mg

Table A.2/ Complete Prevention Rates for the ITT Patients in RANA 3009 (extracted from sponsor's table 16, page 41, volume 2)

	Overall N (%)	Zantac 75mg N (%)	Placebo N (%)	Two-sided p-value of Mantel-Haenzel test stratified by investigators
Number of Patients	274 (100%)	141 (51.46%)	133 (48.54%)	
Complete Prevention	31 (11.31%)	19 (13%)	12 (9%)	0.2446
Not complete Prevention	243 (88.69%)	122 (87%)	121 (91%)	

Table A.4/ Complete Prevention Rates for the ITT Patients in Study 3010 (extracted from sponsor's table 17, page 42, volume 9)

	Overall N (%)	Zantac 75mg N (%)	Placebo N (%)	Two-sided p-value of Mantel-Haenzel test stratified by investigators
Number of Patients	309 (100%)	153 (49.51%)	156 (50.49%)	
Complete Prevention	37 (11.97%)	22 (14%)	15 (10%)	0.1822
Not complete Prevention	272 (88.03%)	131 (86%)	141 (90%)	

Table A.6/ Complete Prevention Rates for the ITT Patients in Study 4005 (extracted from sponsor's Table 18, page 43, volume 9)

	Overall N (%)	Zantac 75mg N (%)	Placebo N (%)	Two-sided p-value of Mantel-Haenzel test stratified by investigators
Number of Patients	269 (100%)	137 (50.93%)	132 (49.07%)	
Complete Prevention	29 (10.78%)	22 (16%)	7 (5%)	0.0058
Not complete Prevention	240 (89.22%)	115 (84%)	125 (95%)	

Copied from Statistical Review and Evaluation for OTC Zantac 75mg dated 8/12/97

Attachment 3: Summary of Number of Subjects withy No Heartburn Following Test Meal for Tagamet HB 200mg

Table 1.2 Number of Subjects with No Heartburn Following Test Meal (per protocol (PP) and ITT populations) in Studies MD-01000 and MD-01001 (Reviewer's table)

Minutes after meal ingestion	ITT/ PP	Study MD-01000				Study MD-01001			
		Proportion (%) Subjects with No Heartburn				Proportion(%) Subjects with No Heartburn			
		Tagamet (%)	Placebo(%)	Diff. T-P(%)	p-value	Tagamet (%)	Placebo (%)	Diff. T-P (%)	p-value
	PP	114/171(67%)	109/168(65%)	2%	.733	136/181 (75 %)	128/182 (70 %)	5%	.35
0	PP	97/171(57%)	90/168(54%)	3%	.586	104/181(57 %)	93/182 (51%))	6%	.25
0	PP	83/171(49%)	84/168(50%)	-1%	.828	82/181 (45 %)	74/182 (41%)	4%	.40
0	PP	90/171(53%)	71/168 (42%)	11%	.065	77/181 (43 %)	57/182 (31%)	12%	.03
20	PP	90/171(53 %)	74/168(45 %)	8%	.128	75/181 (41 %)	61/181(34%)	7%	.16
50	PP	101/171(59%)	76/168(45 %)	14%	.012	84/181 (46 %)	68/182(37%)	9%	.09
80	PP	101/171(59 %)	79/168(47%)	12%	.030	86/181 (48 %)	72/182 (40%)	8%	.14
-180 (primary)	PP ITT	49/171(29 %)* 49/172(29%)*	27/168(16%) 29/173(17%)	13% 12%	.006 .01	44/181(24 %)* 44/182(24 %)*	28/182(15%) 28/183(15%)	9% 9%	.036 .036

Note: *Significant at p-values0.01(Fisher's exact test); P:placebo; T: tagamet; Diff.: difference

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Attachment 4: Summary of Sponsor's ITT Analysis Results for Axid AR 75mg

Sponsor's ITT Analysis Results: Placebo (n=147 for WM-560; n=103 for WM-576) vs Nizatidine Treatment Comparisons

Endpoint/Treatment	Nizatidine 225 mg (n=81)		Nizatidine 75 mg (n=80)		Nizatidine 25 mg (n=95)	
STUDY PROTOCOL # WM-560	Niz - Pla	2-Sided p	Niz - Pla	2-Sided p	Niz - Pla	2-Sided p
Pro-No-H (%)	14	<.001	17	<.001	8	.021
Dur-No-H (Mean)	49.1	<.001	39.9	<.001	18.3	.045
Tot-No-H (Mean)	54.8	<.001	44.9	<.001	18.3	.032
Average Severity (Mean)	-17.9	<.001	-14.7	<.001	-2.9	.097
Worst Severity (Mean)	-29.5	<.001	-28.9	<.001	-4.1	.215
STUDY PROTOCOL # WM-576	n=104		n=101		n=105	
Pro-No-H (%)	11	.003	12	.001	4	.196
Dur-No-H (Mean)	40.1	.001	51.2	<.001	29.4	.004
Tot-No-H (Mean)	44.1	<.001	54.3	<.001	32.7	.002
Average Severity (Mean)	-19.3	<.001	-21.6	<.001	-10.3	<.001
Worst Severity (Mean)	-37.9	<.001	-39.9	<.001	-16.7	<.001

Niz-Pla=(Nizatidine-Placebo) effect size; Results are HFS based; p-values are 2-sided Mantel-Haenszel

Copied from Statistical Review and Evaluation for Axid AP 75mg dated 5/23/95

Attachment 5: Summary of Prmary and Secondary Efficacy Analysis of ITT Population for Axid AR 75mg

Table 1.2 (Reviewer's): Primary and Secondary Efficacy Analyses of ITT Population for study NZ-95-02

End-Points	Plac (n=204)	-15min Axid (n=202)	plac-(-15min Axid)	p-value	0-min Axid (n=203)	plac-(0min Axid)	p-value
% of subjects without post-meal heartburn	11	22	-11	0.002	22	-11	0.004
Average severity of heartburn (mm)	26	20	6	0.002	19	7	0.001
Maximum severity of heartburn (mm)	44	36	8	0.010	34	10	<0.001

Table 1.3 (Reviewer's) : Primary and Secondary Efficacy Analyses of ITT Population at in study NZ-95-03

End-points	plac (n=187)	-15min Axid (n=184)	place-(-15min Axid)	p-value	0min Axid (n=184)	place-0min Axid	p-value
% of subjects without post-meal heartburn	14	19	-5	0.166	27	-13	.001
Average severity of heartburn (mm)	24	19	5	0.006	19	5	.003
Maximum severity of heartburn (mm)	42	33	9	0.004	32	10	.001

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Attachment 6: Summary of Proportion of Patients Reporting No Heartburn Symptoms During the 3 Hours Postmeal for Famotidine 20mg

Study 114

Proportion of Patients Reporting No Heartburn Symptoms During the 3 Hours Postmeal All-Patients-Treated Approach

Treatment Group	No Heartburn	vs. placebo p-value	vs. famotidine 10 mg p-value
Famotidine 20 mg	28/261 (11%)	0.004	0.241
Famotidine 10 mg	21/271 (8%)	0.070	
Placebo	11/262 (4%)		

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Study 117

Proportion of Patients Reporting No Heartburn Symptoms During the 3 Hours Postmeal All-Patients-Treated Approach

Treatment Group	No Heartburn	vs. placebo p-value	vs. famotidine 10 mg p-value
Famotidine 20 mg	185/488 (38%)	< 0.001	0.006
Famotidine 10 mg	147/490 (30%)	0.001	
Placebo	47/249 (19%)		

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Study 128

Proportion of Patients Reporting No Heartburn Symptoms During the 3 Hours Postmeal All-Patients-Treated Approach (N=1332)

Treatment Group	No Heartburn	vs. placebo p-value	vs. famotidine 10 mg p-value
Famotidine 20 mg	219/531 (41%)	< 0.001	0.047
Famotidine 10 mg	190/537 (35%)	0.017	
Placebo	71/264 (27%)		

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/s/

Milton Fan
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-698
Drug Name:	OTC Zantac 150 (ranitidine 150mg) tablet
Indication(s):	Prevention of heartburn (Separate review for treatment of heartburn)
Applicant:	Pfizer Consumer Healthcare
Date(s):	NDA dated October 31, 2003
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II (HFD-715)
Statistical Reviewer:	Milton C. Fan, Ph.D. (HFD-715)
Concurring Reviewers:	Stella Grosser, Ph.D. (HFD-715)
Medical Division:	Gastrointestinal and Coagulant Drug Product (HFD-180)
Clinical Team:	Eric Brodsky, M.D. (HFD-180)
Project Manager:	Diane Moore (HFD-180)

Keywords: clinical study, LOCF, AUC, multiplicity, placebo-controlled

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The sponsor has submitted three placebo-controlled studies (RAN3016, RAN3018, and RAN4006) in support of the proposed claim.

In Study RAN3016, ranitidine 150mg was more effective than placebo in terms of pre-specified primary efficacy endpoint, three clinical endpoints defined by FDA, and 3 of 8 secondary efficacy endpoints (reduction of heartburn severity, peak heartburn severity, and subject global evaluation). For more clinical meaningful clinical endpoint, complete prevention, which was pre-specified as a secondary efficacy endpoint, ranitidine 150mg was not statistically different from placebo.

In Study RAN3018, ranitidine 150mg was not statistically significant different from placebo in terms of pre-specified primary efficacy endpoint, one of three clinical endpoints defined by FDA, and 6 of 7 secondary efficacy endpoints. There was a slight trend in favor of ranitidine 150mg over placebo. For more clinical meaningful clinical endpoint, complete prevention, which was pre-specified as a secondary efficacy endpoint, ranitidine 150mg was not statistically different from placebo.

In Study RAN4006, ranitidine 150mg was statistically significant different from placebo in terms of pre-specified primary efficacy endpoint, three clinical endpoints defined by FDA, and 5 of 8 secondary efficacy endpoints (reduction of heartburn severity, peak heartburn severity, largest number of consecutive timepoints without heartburn, number of timepoints without heartburn, and number of subjects with antacid rescue use). For more clinical meaningful clinical endpoint, complete prevention, ranitidine 150mg was not statistically different from placebo.

In conclusion, two of the three clinical studies (RANA3016 and RANA4006) suggest that ranitidine 150mg was more effective than placebo for reducing severity of meal-induced heartburn when taken right before meal. In the other study (RAN3018), the ranitidine 150mg was not significantly better than placebo for the primary and most secondary efficacy parameters.

1.2 Brief Overview of Clinical Studies

The sponsor has submitted three placebo-controlled efficacy studies (RAN3016, RAN3018, and RAN4006) in support of the proposed claim.

1.2.1 Study RAN3016

This study was a randomized, multicenter (34 sites), double-blind, placebo-controlled, parallel evaluation of ranitidine for reduction of severity or prevention of meal-induced heartburn. This study consisted of four on-site study visits: Prescreening visit, Screening visit, qualifying Run-In Meal visit (Meal 1), and Treatment Meal visit (Meal 2).

The objective of study was to demonstrate the efficacy of ranitidine hydrochloride 75 mg and ranitidine 150mg in reducing the severity of, or preventing meal-induced heartburn in comparison with placebo, when taken immediately prior to consuming a meal that was anticipated to provide heartburn symptoms (heartburn, acid indigestion, sour stomach).

Subject had a history of daily episodes of meal-induced heartburn, at least five days/week over the last two months. In addition, subjects should be able to identify at least two types of food and/or beverage, similar to test meal, which cause their meal-induced heartburn symptoms (heartburn, acid indigestion, sour stomach).

At Visit 1 subject was consented and subsequently entered into a one-week run-in phase where they recorded information a diary card regarding their heartburn episodes, the cause of each episode, level of discomfort rated on 5-point scale (1=very mild; 2=mild; 3=moderate; 4=severe; 5=very severe) and time of treatment for each episode on a daily basis. Subjects returned to the clinic for Visit 2 in 8-34 days for diary card review and if they qualified, provided information for medical and heartburn histories. After this evaluation, subjects who qualified reported back to the designated meal site within 34 days for Meal 1 (Visit 3).

To qualify for Meal 1 (Visit 3), subjects should:

- have recorded experiencing meal-induced heartburn on at least four out of seven consecutive days on their run-in diary card.
- have $\geq$ 60% of all meal-induced episodes rated as moderate, severe, or very severe (3 or above on a 5-point scale measuring discomfort level).
- meet all other selection criteria evaluated at Visit 2.

To qualify for the treatment phase Meal 2 (Visit 4), subject should:

- have a discomfort level of $\leq$10 mm on a VAS prior to dosing
- have developed heartburn symptoms (heartburn, acid indigestion, sour stomach) and reached a discomfort level of $\geq$34 mm on a VAS within the first 90 minutes of completing Meal 1 and prior to rescue antacid use.

Those subjects who qualified for Meal 2 (Visit 4) were randomized to either of placebo, ranitidine 75mg, and ranitidine 150mg.

Subjects were allowed to take rescue antacid, Maalox, if they requested it.

The primary efficacy endpoint was the heartburn severity measured by area under the curve (AUC). Each subject's VAS measurements throughout the entire 4-hour and 40-minutes recording period was used to calculate an AUC for that subject using the trapezoidal rule. Pairwise comparisons of means of the individual AUCs were performed between treatment groups using an analysis of variance (ANOVA) model with treatment and investigator terms.

The secondary efficacy endpoints were reduction of heartburn severity, peak heartburn severity, duration without symptoms, global evaluation of medication effectiveness and associated gastrointestinal symptoms, need for antacid rescue, time to antacid rescue, complete prevention, extended reduction of severity or prevention of heartburn symptoms, and nocturnal heartburn symptoms.

The "Intent-to-Treat" population was to include all subjects who at the Treatment Meal visit were randomized and consumed both the double-blind study drug and the Treatment Meal. The Intent-to-Treat population was to be the primary population for all efficacy, safety, and demographic analysis.

Subjects were to be included in the "Efficacy Evaluable" population if they completed a seven day Screen diary; met all of the entry criteria; gave informed consent; followed instructions with respect to medications, food, and drink; took study drug according to the protocol; had a VAS score $\leq$10mm prior to both meals; had a VAS score $\geq$34mm within the first 90 minutes following the Run-In Meal visit and prior to using rescue antacid; consumed the same portions at the Treatment Meal visit as at the Run-In Meal visit; and completed the heartburn evaluation just prior to and at the end of each meal. If >10% of subjects did not meet the above definition of efficacy evaluability, then the primary analysis was to be repeated on the evaluable subset (i.e., Efficacy Evaluable population) to supplement the Intent-to-Treat results.

For any efficacy parameter, the ranitidine 150mg group was to be considered superior to the ranitidine 75mg group if the ranitidine 150mg group was statistically significant 'better' than the placebo group and if the ranitidine 75mg and placebo groups were not significantly different from one another. Alternative, if both ranitidine treatment groups were significantly more efficacious than placebo, then the ranitidine 150mg group must also reveal significantly greater efficacy than the ranitidine 75mg group to be considered its superior.

A clinical significant effect was defined as a treatment difference from placebo in Meal 2 heartburn severity of 20 mm·hr, as measured by area under the curve over the 4-hour and 40-minutes evaluation period. Assuming a standard deviation of 86mm, a sample size of 306 subjects per arm provided 80% power to detect differences at the two-sided 5% level. Since all pairwise comparisons were of interest, a Bonferroni-Holm adjustment was used to perform sample size calculations. The application of this Bonferroni-Holm adjustment was performed in a hierarchical fashion. Each of the active treatments was first compared to placebo at an $\alpha/2$ (0.025) level of significance. If either of these two active treatments was statistically significantly superior to placebo, the two active treatments were compared at a 0.05 level of significance.

Per the protocol amendment, three pairwise comparisons could be performed for each parameter: ranitidine 150mg vs. placebo; ranitidine 75mg vs. placebo; and ranitidine 150mg vs. ranitidine 75mg. First, ranitidine 150mg was compared to placebo at the α=0.05 level of significance. Second, only if the first comparison was statistically

significant, then ranitidine 75mg was compared to placebo at the α=0.05 level of significance. Third, if both of these two comparisons were statistically significant, the final comparison between ranitidine 150mg and ranitidine 75mg was performed at the α=0.05 level of significance.

Two thousand seven hundred eighty-four (2,784) adult outpatients participated in the single-blind Run-In Phase of the study. Nine hundred sixty-two (962) subjects successfully completed the Run-In Phase, were randomized to treatment, and entered the Treatment Phase of the study (320 ranitidine 75mg, 320 ranitidine 150mg, 322 placebo).

Among 962 randomized subjects, 961 subjects completed the Treatment Meal visit. One subject from the ranitidine 75mg treatment group was prematurely discontinued due to an adverse event.

A total of 198 subjects (80 in ranitidine 75mg, 67 in ranitidine 150mg and 51 in placebo) deviated from the study protocol and were excluded from the Efficacy Evaluable population. The three most common reasons for the exclusion of subjects from the Efficacy Evaluable population were: (1) heartburn severity >10mm prior to Treatment Meal; (2) insufficient heartburn discomfort (VAS score <34mm) within the first 90 minutes follow the Run-In Meal, and (3) failure to consume the same portions at both meals.

1.2.2 Study RAN3018

This study was a randomized, multicenter (36 sites), double-blind, placebo-controlled, parallel evaluation of ranitidine for reduction of severity or prevention of meal-induced heartburn.

The study design of this study was similar to that for the Study RAN3016 with some exceptions listed below.

Main criteria for inclusion included: to participate in this study subject should have achieved relief of heartburn symptoms through the use of antacids during the last six months.

The primary efficacy endpoint included prevention of success - clinical endpoint in addition to heartburn severity – AUC.

The criteria of "or subjects had experienced complete prevention" was added to three clinical endpoints.

Time for the criteria for first clinical endpoint had changed from 40 minutes to 45 minutes for decreasing in AUC from the Run-In to the Treatment Meal visit.

The secondary efficacy endpoints did not include need for antacid rescue and time to antacid rescue.

OTC H_2 antagonists might be used to treat heartburn between Meal 1 (Visit 3) and Meal 2 (Visit 4).

Subjects who took rescue antacid within 90 minutes of the scheduled completion time of Meal 1 (12:30 pm) prior to reaching a discomfort level of ≥34mm was not disqualified after Meal 1 and prior to Meal 2 (Visit 4)

Antacid use was not assessed.

The heartburn severity score prior to meal was not assessed for protocol compliance.

If the primary endpoint (Heartburn Severity – AUC) showed that ranitidine 150mg was significant better than placebo, further analyses were performed to investigate the clinical meaningfulness of the result. This was in response to the FDA's interest expressed during a meeting held on July 18, 1997, requesting subject success/failure rates based on dichotomous endpoints, to provide consumers with efficacy information that is easier to understand.

Three separate clinical definition of success were explored, each related to the primary endpoint of heartburn AUC. The first clinical endpoint of interest defined subjects as being a treatment success if they had an average post-meal VAS score at Meal 2 of 17 mm or less. The second defined a subject as being a treatment success if they showed a decrease in AUC from Meal 1 to Meal 2 of 20 or more mm·hr or experienced complete prevention. The third clinical endpoint defined subjects as treatment success if their Meal 2 AUC is 50% or less than their Meal 1 AUC.

A composite score was created, as the number of these three clinical definitions on which a subject was declared successful. This composite score, also known as the O'Brien method, acted as an overall test of clinical difference between the treatments. If ranitidine 150mg was significantly different from placebo for this overall composite score, then each clinical success component was analyzed separately to assess the clinical significance.

Pairwise comparisons between treatment groups were done in a stepdown hierarchical manner. Since the ranitidine 150mg vs. placebo was the comparison of most interest, and was expected to be the largest, this difference was tested at the alpha=0.05 level. If this value was less than or equal to 0.05, the other two pairwise comparisons (ranitidine 75mg vs. placebo and ranitidine 150mg vs. ranitidine 75mg) was made, each at the alpha=0.05 level.

The secondary efficacy endpoints did not include need for antacid rescue and time to antacid rescue.

Three thousand one hundred seventy (3,170) subjects returned the seven day Screening diary. Nine hundred twenty-one (921) subjects successfully completed the Run-In Phase,

were randomized to treatment, and entered the Treatment Phase of the study (309 ranitidine 75mg, 306 ranitidine 150mg, and 306 placebo).

Among 921 randomized subjects, 918 subjects completed the Treatment Meal visit. Three subjects prematurely discontinued from the study. Two subjects, one each in the placebo and ranitidine 75mg treatment groups, discontinued due to an adverse events. One subject in the ranitidine 150mg group discontinued due to non-compliance with the protocol.

A total of 135 subjects (51 in ranitidine 75mg, 45 in ranitidine 150mg and 39 in placebo) deviated from the study protocol and were excluded from the Efficacy Evaluable population. The three most common reasons for the exclusion of subjects from the Efficacy Evaluable population were: (1) insufficient heartburn discomfort (VAS score <34mm) within the first 90 minutes follow the Run-In Meal, (2) heartburn severity >10mm prior to Treatment Meal; and (3) failure to consume the same portions at both meals.

1.2.3 Study RAN4006

This study was a randomized, multicenter (23 sites), double-blind, placebo-controlled, parallel evaluation of ranitidine for reduction of severity or prevention of meal-induced heartburn.

The study design of this study was similar to that for the Study RAN3016 with some exceptions listed below.

Subjects who met the minimum requirements at the Run-In Meal visit were scheduled to return for the Treatment Meal visit within 4 to 16 days after the Run-In Meal visit.

Subject returned to clinic between 8 and 26 days from their prescreening visit for diary card review.

At the conclusion of the Treatment Meal evaluation period, subjects were not given a diary card to record any new post-Treatment Meal heartburn episodes, the cause, time and day of the week of episode, level of discomfort and if they treated the episode. .

Exclusion criteria did not include:

a.The subject had ever taken omeprazole or lansoprazole.
b.The subject was a current methadone user
c.The subject had history of allergies to any portion of the test meal.

Secondary efficacy endpoints did not include longest duration of no heartburn, total duration of no heartburn, complete prevention, extended reduction of severity or prevention of heartburn symptoms, and nocturnal heartburn symptoms.

For duration with symptoms, the longest duration of complete prevention was assessed.

The global question: "From the time you took your medication until now, how would you rate the discomfort level you experienced due to each of the following 11 symptoms?" was not included.

The pairwise comparisons were performed in a hierarchical fashion. Each of the active treatments with was first compared to placebo at an $\alpha/2$ (0.025) level of significance (Boneferrroni-Holm adjustment). If both active treatments were statistically significantly superior to placebo, the two active treatments were compared at a 0.05 level of significance.

In the sample size determination, assuming a standard deviation of 60mm, sample size of 192 subjects per arm was needed.

Based on discussion with the FDA (meeting of 18 July, 1997), additional endpoints that provide consumer-meaningful outcome measures were included in the protocol amendment. These endpoints were similar to those generated in clinical studies with other OTC H_2-receptor antagonists. These clinical endpoints categorize study treatment effect on a per subject basis of either success or failure are all related to the primary endpoint of heartburn severity as measured by the AUC.

Each subject's response to treatment was categorized for each of the following three dichotomous clinical endpoints:

- Reduction by 40 mm·hour or more in heartburn severity AUC from Run-In to Treatment Meal visits
- Reduction by 50% or more in heartburn severity AUC from Run-In to Treatment Meal visits
- Average Post-Treatment Meal LOCF heartburn severity scores of 17 mm or less

Furthermore, for each clinical endpoint, a subject who achieved complete prevention of heartburn severity at all post-Treatment Meal visit evaluations was classified as a "success', whereas a subject who used rescue antacid during the Treatment Meal visit was classified as a "failure." In addition, for the dichotomous endpoints, a 10% point difference between an active treatment and placebo was declared as a clinically meaningful difference.

A composite score was calculated as the sum of three clinical definitions on which a subject was declared a success. If ranitidine 150mg was significantly different from placebo at this overall level, each component was analyzed separately for clarification of clinical effect.

The "Number of Subjects with Complete Prevention" analysis was inadvertently omitted by sponsor from this study protocol but had been used as a secondary efficacy endpoint in previous meal-induced heartburn studies. Two other analyses related to the complete

prevention endpoint ("Largest Number of Consecutive Timepoints without Heartburn" and "Number of Timepoints without Heartburn") were included.

Two thousand nine hundred forty-nine (2,949) subjects returned the diary. Six hundred one (601) subjects successfully completed the Run-In Phase, were randomized to treatment, and entered the Treatment Phase of the study (204 ranitidine 75mg, 198 ranitidine 150mg, and 199 placebo).

All if these subjects completed the Treatment Meal and there were no premature discontinuations from the study.

A total of 115 subjects (51 in ranitidine 75mg, 35 in ranitidine 150mg and 29 in placebo) deviated from the study protocol and were excluded from the Efficacy Evaluable population. The three most common reasons responsible for exclusion of subjects from the Efficacy Evaluable population were: (1) insufficient heartburn discomfort (VAS core <34mm) within the first 90 minutes following the Run-In Meal; (2) failure to consume the same number of portions at both meals; and (3) having a heartburn severity VAS score >10mm just prior to eating the Run-In Meal.

1.3 Statistical Issues and Findings

In both studies (RAN3016 and RAN4006), it was stated in the protocol that the application of this Bonferroni-Holm adjustment was performed in a hierarchical fashion. Each of the active treatments was first compared to placebo at an $\alpha/2$ (0.025) level of significance. If either of these two active treatments was statistically significantly superior to placebo, the two active treatments were compared at a 0.05 level of significance.

For study RAN3016, per the protocol amendment, three pairwise comparisons could be performed for each parameter: ranitidine 150mg vs. placebo; ranitidine 75mg vs. placebo; and ranitidine 150mg vs. ranitidine 75mg. First, ranitidine 150mg was compared to placebo at the α=0.05 level of significance. Second, only if the first comparison was statistically significant, then ranitidine 75mg was compared to placebo at the α=0.05 level of significance. Third, if both of these two comparisons were statistically significant, the final comparison between ranitidine 150mg and ranitidine 75mg was performed at the α=0.05 level of significance.

Furthermore, for study RAN3018, it was pre-specified in the protocol to use a stepdown hierarchical method for multiplicity. Pairwise comparisons between treatment groups were done in a stepdown hierarchical manner. Since the ranitidine 150mg vs. placebo was the comparison of most interest, and was expected to be the largest, this difference was tested at the alpha=0.05 level. If this value was less than or equal to 0.05, the other two pairwise comparisons (ranitidine 75mg vs. placebo and ranitidine 150mg vs. ranitidine 75mg) was made, each at the alpha=0.05 level.

In both studies (RAN3016 and RAN3018), it was stated the final study report to define "ranitidine 150mg was considered superior to ranitidine 75mg." For any efficacy parameter, the ranitidine 150mg group was to be considered superior to the ranitidine 75mg group if the ranitidine 150mg group was statistically significant 'better' than the placebo group and if the ranitidine 75mg and placebo groups were not significantly different from one another. Alternative, if both ranitidine treatment groups were significantly more efficacious than placebo, then the ranitidine 150mg group must also reveal significantly greater efficacy than the ranitidine 75mg group to be considered its superior.

The only comparisons of interest for this review are ranitidine 150mg versus placebo and ranitidine 150mg versus ranitidine 75mg. The p-values for ranitidine 150mg vs. placebo and ranitidine 150mg vs. ranitidine 75mg comparisons are shown to confirm that the testing procedure was followed.

For the pre-specified primary endpoint, heartburn severity AUC, study RAN3016 showed that at the Treatment Meal visit, that there was a statistically significant difference in mean heartburn severity AUC between the ranitidine 150mg and placebo treatment groups for both Intent-to-Treat and efficacy evaluable populations. The treatment differences of means between ranitidine 150mg and placebo were 20.1 mm·hr and 16.9 mm·hr for Intent-to-Treat and efficacy evaluation populations, respectively.

There was no statistically significant difference between the ranitidine 150mg and ranitidine 75 groups. The treatment differences of means between ranitidine 150mg and ranitidine 75mg were 0.6 mm·hr and 1.4 mm·hr in favor of ranitidine 75mg group for Intent-to-Treat and efficacy evaluation populations, respectively.

Study RAN3018 indicated that at the Treatment Meal visit, there was no statistically significant difference in mean heartburn severity AUC between the ranitidine 150mg and placebo treatment groups for both Intent-to-Treat and efficacy evaluable populations. The treatment differences of means between ranitidine 150mg and placebo were 4.2 mm·hr and 6.9 mm·hr for Intent-to-Treat and efficacy evaluation populations, respectively.

There was no statistically significant difference between the ranitidine 150mg and ranitidine 75mg groups. The treatment differences of means between ranitidine 150mg and ranitidine 75mg were 6.0 mm·hr and 1.1 mm·hr in favor of ranitidine 75mg group for Intent-to-Treat and efficacy evaluation populations, respectively.

Study RAN4006 showed that at the Treatment Meal visit, there was a statistically significant difference in mean heartburn severity AUC between the ranitidine 150mg and placebo treatment groups for all subjects population. But, for efficacy evaluable population, at the Treatment Meal visit, mean heartburn severity AUC of the ranitidine 150mg group was numerically lower than that of placebo. It failed to achieve statistical significance level of 0.025. The treatment differences of means between ranitidine 150mg and placebo were 21.2 mm·hr and 16.3 mm·hr for Intent-to-Treat and efficacy evaluation populations, respectively.

There was no statistically significant difference between the ranitidine 150mg and ranitidine 75mg groups. However, there was a trend for all three clinical endpoints in favor of ranitidine 150mg over ranitidine 75mg in the all subjects population (p=0.102) not in the efficacy evaluable population (p=0.563). The treatment differences of means between ranitidine 150mg and ranitidine 75mg were 12.1 mm·hr and 5.5 mm·hr for Intent-to-Treat and efficacy evaluation populations, respectively.

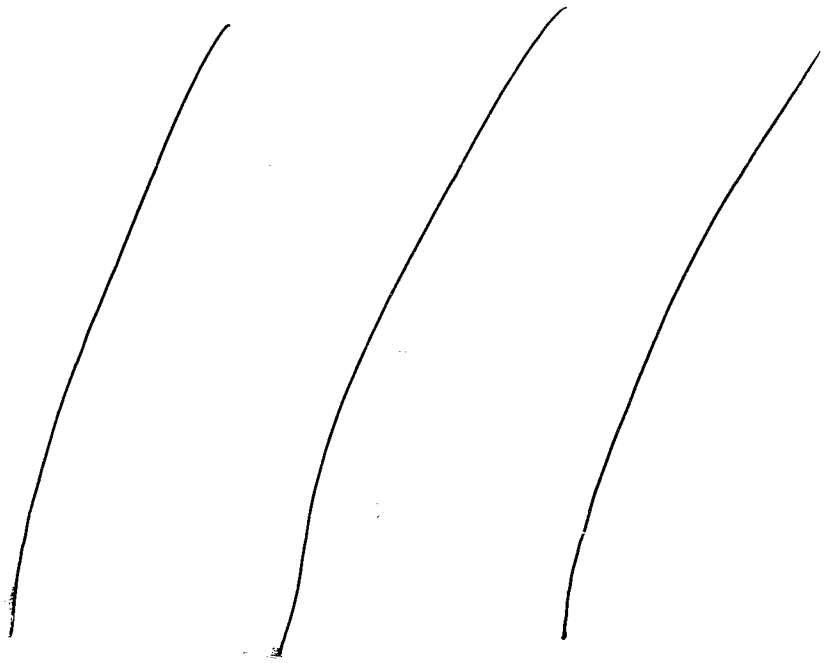
2. INTRUDUCTION

2.1 Overview

Over-the-Counter (OTC) Zantac 75 (Ranitidine 75mg tablet) was approved in December 19, 1995 for relief of heartburn. OTC Zantac 75 was approved in June 8, 1998 for the prevention of heartburn.

In the current NDA, the sponsor seeks approval of the Over-the-Counter (OTC) use of Zantac 150 (Ranitidine Tablet 150 mg) for the prevention of heartburn

The sponsor has submitted three Phase III studies: (RAN3016, RAN3018 and RAN4006) in support of the prevention of heartburn.



This review will address the comparisons between ranitidine 150mg and placebo and between ranitidine 150mg and ranitidine 75mg.

This review addresses only the prevention of heartburn. A separate review will address the treatment of heartburn.

2.2 Data Sources

The sponsor has submitted three Phase III studies: (RAN3016, RAN3018 and RAN4006) supporting the prevention of heartburn. These studies include:

RAN3016: A Randomized, Double-blind, Double-dummy, Placebo-controlled, Parallel Evaluation of Ranitidine for the Reduction of Severity or Prevention of Meal-induced Heartburn

RAN3018 : A Randomized, Double-blind, Double-dummy, Placebo-controlled, Parallel Evaluation of Ranitidine for the Reduction of Severity or Prevention of Meal-induced Heartburn

RAN4006: A Randomized, Double-blind, Double-dummy Placebo-controlled, Parallel Evaluation of Ranitidine for the Reduction of Severity or Prevention of Meal-induced Heartburn

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study RAN3016

3.1.1.1 Study Design

This study was a randomized, multicenter (34 sites), double-blind, placebo-controlled, parallel evaluation of ranitidine for reduction of severity or prevention of meal-induced heartburn. The study consisted of four on-site study visits: Prescreening visit, Screening visit, qualifying Run-In Meal visit (Meal 1), and Treatment Meal visit (Meal 2).

The objective of study was to demonstrate the efficacy of ranitidine hydrochloride 75 mg and ranitidine 150mg in reducing the severity of, or preventing meal-induced heartburn in comparison with placebo, when taken immediately prior to consuming a meal that was anticipated to provide heartburn symptoms (heartburn, acid indigestion, sour stomach).

Subject had a history of daily episodes of meal-induced heartburn, at least five days/week over the last two months. In addition, subjects should be able to identify at least two types of food and/or beverage, similar to test meal, which cause their meal-induced heartburn symptoms (heartburn, acid indigestion, sour stomach).

At Visit 1 subject was consented and subsequently entered into a one-week run-in phase where they recorded information a diary card regarding their heartburn episodes, the cause of each episode, level of discomfort rated on 5-point scale (1=very mild; 2=mild; 3=moderate; 4=severe; 5=very severe) and time of treatment for each episode on a daily basis. Subjects returned to the clinic for Visit 2 in 8-34 days for diary card review and if they qualified, provided information for medical and heartburn histories. After this evaluation, subjects who qualified reported back to the designated meal site within 34 days for Meal 1 (Visit 3).

To qualify for Meal 1 (Visit 3), subjects should:

- have recorded experiencing meal-induced heartburn on at least four out of seven consecutive days on their run-in diary card.
- have $\geq$ 60% of all meal-induced episodes rated as moderate, severe, or very severe (3 or above on a 5-point scale measuring discomfort level).
- meet all other selection criteria evaluated at Visit 2.

To qualify for the treatment phase Meal 2 (Visit 4), subject should:

- have a discomfort level of $\leq$10 mm on a VAS prior to dosing
- have developed heartburn symptoms (heartburn, acid indigestion, sour stomach) and reached a discomfort level of $\geq$34 mm on a VAS within the first 90 minutes of completing Meal 1 and prior to rescue antacid use.

Subjects consumed an identical meal at both Meal 1 (Visit 3) and Meal 2 (Visit 4). They took assigned study medication just prior to each meal. The allotted time for completion of each of the meals was 40 minutes. Subjects from Meal 1 who qualified for Meal 2 returned for Meal 2 no earlier than four days and no later than 22 days after consuming Meal 1.

At both meals subjects responded to the question, "Do you have heartburn symptoms (heartburn, sour stomach, acid indigestion) at this time?" just prior to the beginning of the meal, 40 minutes later (at the end of the meal), and at 15-minute intervals thereafter for a total of 4 hours and 40 minutes from the time of dosing. At those same time intervals, if the subject responded "yes" to having heartburn symptoms (heartburn, acid indigestion, sour stomach), the subject placed a vertical mark on a 100 mm Visual Analog Scale (VAS) indicating the level of discomfort he/she was expecting. Global evaluation was made at the end of the 4-hour and 40 minutes evaluation period.

At the conclusion of Meal 2, subjects were given a diary card to record any post-Meal 2 heartburn episodes, the cause, time and day of each episode, level of discomfort rated on 5-point scale and if they treated the episode. In addition, they responded to the following questions: "Did your heartburn keep you from falling asleep last night?", "Did your heartburn wake you from sleep last night?" and "Did you experience heartburn upon awakening?"

Once enrolled, each subject was in the study for a maximum of eight weeks and had a total of four visits.

Subjects who qualified for Meal 1 (Visit 1) received single-blind study medication (2 placebo tablets matched to ranitidine 75mg and ranitidine 150mg, respectively). Those subjects who qualified for Meal 2 (Visit 2) were randomized to either of placebo, ranitidine 75mg, and ranitidine 150mg.

Subjects were allowed to take rescue antacid, Maalox, if they requested it.

The primary efficacy endpoint was the heartburn severity measured by area under the curve (AUC). Each subject's VAS measurements throughout the entire 4-hour and 40-minutes recording period was used to calculate an AUC for that subject using the trapezoidal rule. Pairwise comparisons of means of the individual AUCs was performed between the treatment groups using an analysis of variance (ANOVA) model with treatment and investigator terms.

The secondary efficacy endpoints were reduction of heartburn severity, peak heartburn severity, duration without symptoms, global evaluation of medication effectiveness and associated gastrointestinal symptoms, need for antacid rescue, time to antacid rescue, complete prevention, extended reduction of severity or prevention of heartburn symptoms, and nocturnal heartburn symptoms.

Various secondary efficacy analyses listed below were also done to confirm and support the primary analysis:

(1) Reduction of Heartburn Severity

Each subject was assigned a 'percent reduction' score based on subtracting the heartburn severity AUC at Meal 2 (Treatment Meal) from the heartburn severity AUC at Meal 1 (Run-In Meal) and then dividing by the Meal 1 AUC. Means of these scores was then compared between treatments using ANOVA methods.

(2) Peak Heartburn Severity

Each subject's highest VAS score post-meal was determined. The median of the individual peak scores were compared between treatments using the van Elteren test. In addition, percent reduction in peak heartburn severity from Meal 1 to Meal 2 was analyzed.

(3) Duration without Symptoms

(i) Longest Duration of Complete Prevention

Each subject was assigned a value based on the number of minutes after the meal at which the first 'yes' response occurred to the question "Do you have heartburn symptoms

at this time?" Median durations were calculated after assigning each subject the midpoint of the interval during which the heartburn began. Median durations were then compared between treatments using the van Elteren test. Subjects who did not develop heartburn during the meal session were assigned the maximum value (240 minutes). Only subjects who reported no heartburn symptoms at the beginning of the meal were included in this analysis.

(ii) Longest Duration of No Heartburn

Longest duration of no heartburn was defined as the maximum number of consecutive post-meal timepoints at which a subject recorded an answer of "No" to the question. "Do you have heartburn symptoms at this time?" Median durations were then compared between treatments using the van Elteren test.

(iii) Total Duration of No Heartburn

Total duration of no heartburn was defined as the proportion of post-meal timepoints at which the subject recorded an answer of "No" to the question, "Do you have heartburn symptoms at this time?" Median durations were then compared between treatments using the van Elteren test.

(4) Global Evaluations

At the end of each meal session (4-hour and 40 minutes), responses to two global questions were obtained by asking subjects to respond to each of the following questions:

(i) "How would you rate the effectiveness of the study medication?":

Effectiveness Scores
0=Not Effective
1=Poor
2=Fair
3=Good
4=Very Good
5=Excellent

The distributions of these scores were compared between treatments using the van Elteren test.

(ii) "From the time you took your medication until now, how would you rate the discomfort level you experienced due to each of the following 11 symptoms?"

Acid indigestion	Burning feeling	Sour stomach
Acid reflux	Gas	Stomach ache/pain
Acid taste	Heartburn	Stomach fullness/bloating
Belching/burping	Indigestion	

Effectiveness Scores
0=None
1=Very Mild
2=Mild
3=Moderate
4=Severe
5=Very Severe

The distributions of these scores were compared between treatments using the van Elteren test.

(5) Need for Antacid Rescue

The proportion of subjects needing antacid rescue was compared between treatments using the Mantel-Haenzel test.

(6) Time to Antacid Rescue

For subjects who rescued, the mean time to rescue was compared between treatments using ANOVA methods.

(7) Complete Prevention

A subject who reported having no heartburn symptoms at all post-meal timepoints was considered to have experienced complete prevention of heartburn. The proportion of subjects with complete prevention was compared between treatment groups using the Mantel-Haenszel test.

For any efficacy parameter, the ranitidine 150mg group was to be considered superior to the ranitidine 75mg group if the ranitidine 150mg group was statistically significant 'better' than the placebo group and if the ranitidine 75mg and placebo groups were not significantly different from one another. Alternative, if both ranitidine treatment groups were significantly more efficacious than placebo, the ranitidine 150mg group must also reveal significantly greater efficacy than the ranitidine 75mg group to be considered its superior.

A clinical significant effect was defined as a treatment difference from placebo in Meal 2 heartburn severity of 20 mm·hr, as measured by area under the curve over the 4-hour and 40-minutes evaluation period. Assuming a standard deviation of 86mm, a sample size of 306 subjects per arm provided 80% power to detect differences at the two-sided 5% level.

Since all pairwise comparisons were of interest, a Bonferroni-Holm adjustment was used to perform sample size calculations. The application of this Bonferroni-Holm adjustment was performed in a hierarchical fashion. Each of the active treatments was first compared to placebo at an $\alpha/2$ (0.025) level of significance. If either of these two active treatments

was statistically significantly superior to placebo, the two active treatments were compared at a 0.05 level of significance.

The original protocol was amended to include 1) a modification to the Bonferroni-Holm adjustment used in the efficacy analysis; 2) a modification of the method of consistency adjustment between the symptom and severity ratings; 3) an incorporation of the use of rescue antacid into the calculation of LOCF severity values; 4) the addition of the Run-In Meal heartburn severity AUC as a factor in the statistical analysis of the primary endpoint; 5) analysis of the clinically meaningful endpoints of success and failure, using three different criteria; 6) an additional efficacy parameter, reduction of heartburn severity.

Per the protocol amendment, three pairwise comparisons could be performed for each parameter: ranitidine 150mg vs. placebo; ranitidine 75mg vs. placebo; and ranitidine 150mg vs. ranitidine 75mg. First, ranitidine 150mg was compared to placebo at the α=0.05 level of significance. Second, only if the first comparison was statistically significant, then ranitidine 75mg was compared to placebo at the α=0.05 level of significance. Third, if both of these two comparisons were statistically significant, the final comparison between ranitidine 150mg and ranitidine 75mg was performed at the α=0.05 level of significance.

3.1.1.2 Sponsor's Analysis

Two thousand seven hundred eighty-four (2,784) adult outpatients participated in the single-blind Run-In Phase of the study. Nine hundred sixty-two (962) subjects successfully completed the Run-In Phase, were randomized to treatment, and entered the Treatment Phase of the study (320 ranitidine 75mg, 320 ranitidine 150mg, 322 placebo).

Among 962 randomized subjects, 961 subjects completed the Treatment Meal visit. One subject from the ranitidine 75mg treatment group was prematurely discontinued due to an adverse event.

A total of 198 subjects (80 in ranitidine 75mg, 67 in ranitidine 150mg and 51 in placebo) deviated from the study protocol and were excluded from the Efficacy Evaluable population. The three most common reasons for the exclusion of subjects from the Efficacy Evaluable population were: (1) heartburn severity >10mm prior to Treatment Meal; (2) insufficient heartburn discomfort (VAS score <34mm) within the first 90 minutes follow the Run-In Meal, and (3) failure to consume the same portions at both meals.

3.1.1.2.1 Planned Analysis

All subjects who are dispensed study medication at Meal 2 (Visit 4) comprised the Intent-to-Treat population.

The LOCF method was used to replace missing and non-meaningful heartburn severity VAS score. For both primary and secondary analyses, for any time points at which no score was indicated or after antacid rescue had been taken, the previous observation was carried forward to fill in the missing data, with two exceptions. If the evaluation at the pre-meal timepoint (Time 0 minutes) was missing, no score would be available to be carried forward to impute this missing value. If the evaluation at the end of the meal (40 minutes after dosing) was missing, the evaluation just prior to the meal (0 minutes after dosing) was not carried forward. This patient's data was not included in the primary efficacy analysis or in any analysis where Area Under the Curve (AUC) was the measurement of interest.

As a consequence of this procedure, if a subject used rescue antacid prior to the first post-meal observation, all post-meal severity scores were to be set to missing and no severity score was be carried forward.

The "Intent-to-Treat" population was to include all subjects who at the Treatment Meal visit were randomized and consumed both the double-blind study drug and the Treatment Meal. The Intent-to-Treat population was to be the primary population for all efficacy, safety, and demographic analysis.

Subjects were to be included in the "Efficacy Evaluable" population if they completed a seven day Screen diary; met all of the entry criteria; gave informed consent; followed instructions with respect to medications, food, and drink; took study drug according to the protocol; had a VAS score $\leq$10mm prior to both meals; had a VAS score $\geq$34mm within the first 90 minutes following the Run-In Meal visit and prior to using rescue antacid; consumed the same portions at the Treatment Meal visit as at the Run-In Meal visit; and completed the heartburn evaluation just prior to and at the end of each meal. If >10% of subjects did not meet the above definition of efficacy evaluability, then the primary analysis was to be repeated on the evaluable subset (i.e., Efficacy Evaluable population) to supplement the Intent-to-Treat results.

Two revisions to the calculation of LOCF heartburn severity were prescribed in the protocol amendment. First, the aforementioned consistency adjustment between symptom rating and severity scores (i.e., if symptom='N' then severity=0) was changed to account for non-missing severity ratings at times when subjects identified themselves as having no symptoms. Because it could not be determined whether the symptom indicator or severity score was incorrect, neither value was changed. The second revision was to compare the severity rating immediately preceding the use of rescue antacid to all subsequent severity ratings and to replace only those values that were less than the pre-rescue antacid, comparison value.

It was determined that using the LOCF methodology for only the severity scores created an inconsistency between those variables derived from severity scores and those derived from symptom indicators. It was therefore decided that a similar LOCF methodology should be applied to the heartburn symptom indicators as well. The methodology was as follows. First, all symptom indicators following the use of rescue antacid were assigned a

value of "Yes." This replacement was necessary because symptom indicators following the use of antacid were not directly interpretable. Second, if the heartburn symptom indicator was missing, but the LOCF severity score was non-missing, the symptom indicator was adjusted to correspond to the severity score (e.g., symptom indicators would be set to "Yes" if their corresponding LOCF severity scores were greater than zero). Third, symptom indicators that remained missing after this imputation received the value of the most immediately preceding, non-missing symptom indicator. If, however, the 40-minutes observation (the first post-meal observation) was missing, the indicator at time zero was not imputed into this observation.

Based on discussion with the FDA (meeting of 18 July, 1997), additional endpoints that provide consumer-meaningful outcome measures were included in the protocol amendment. These endpoints were similar to those generated in clinical studies with other OTC H_2-receptor antagonists. These clinical endpoints categorize study treatment effect on a per subject basis of either success or failure were all related to the primary endpoint of heartburn severity as measured by the AUC.

Each subject's response to treatment was categorized for each of the following three dichotomous clinical endpoints:

- Reduction by 40 mm·hour or more in heartburn severity AUC from Run-In to Treatment Meal visits
- Reduction by 50% or more in heartburn severity AUC from Run-In to Treatment Meal visits
- Average Post-Treatment Meal LOCF heartburn severity scores of 17 mm or less

Furthermore, for each clinical endpoint, a subject who achieved complete prevention of heartburn severity at all post-Treatment Meal visit evaluations was classified as a "success', whereas a subject who used rescue antacid during the Treatment Meal visit was classified as a "failure." In addition, for the dichotomous endpoints, a 10% point difference between an active treatment and placebo was declared as a clinically meaningful difference.

A composite score was calculated as the sum of three clinical definitions on which a subject was declared a success. If ranitidine 150mg was significantly different from placebo at this overall level, each component was analyzed separately for clarification of clinical effect.

Reduction of Heartburn Severity

Additionally, for each subject, the reduction of heartburn severity was calculated by subtracting the Treatment Meal heartburn severity AUC from the Run-In Meal AUC.

Number of Subjects with Complete Prevention

Individuals who used rescue antacid were necessarily identified as treatment failures. Furthermore, only subjects who reported no heartburn symptoms at the start of the meal were included in this analysis. The complete prevention endpoint was compared across treatment groups using the Mantel-Haenszel test stratified by investigator.

Duration without Heartburn Symptoms

The original definition of this endpoint was adjusted to account for the use of antacid rescue. The duration without heartburn symptoms was calculated from dosing rather than from end of meal. Consequently, duration without heartburn symptoms was calculated by counting the number of minutes from dosing until the first of either a LOCF symptom value of "Yes" or the use of rescue antacid.

Largest Number of Consecutive Timepoint without Heartburn

The largest number of consecutive 15-minute post-meal timepoints (40 minutes post-meal to 280 minutes; for a total of 17 timepoints) at which the LOCF heartburn symptom indicator had a value of 'No' was calculated for each subject. The median number of timepoints was compared for treatment group difference using Wilcoxon rank sum test stratified by investigator (van Elteren test).

Number of Timepoints without Heartburn Symptoms

The total number of 15-minute post-meal timepoints (40 minute post-meal to 280 minutes; for a total of 17 timepoints) at which the LOCF heartburn symptom indicator had a value of "No" was calculated for each subject. The median number of timepoints was compared for treatment group difference using Wilcoxon rank sum test stratified by investigator (van Elteren test).

3.1.1.2.2 Treatment Group Comparability

A summary of the number of patients by baseline characteristics by treatment group is given in Appendix Table 1.

As seen from Appendix Table 1, the treatment groups appeared similar with regard to all baseline characteristics with one exception. There was a statistically significant difference between the treatment groups for the number of days per week that subjects reported experiencing meal-related episodes of heartburn over the preceding two months. The number of days reported for the ranitidine 150mg (5 days: 32%; 6 days: 23%; 7 days: 45%) was statistically significantly higher (p=0.037) than the ranitidine 75mg (5 days: 39%; 6 days: 24%; 7 days: 37%).

3.1.1.2.3 Sponsor's Analysis of Primary Efficacy Variable

The primary efficacy endpoint was the heartburn severity area under the curve (AUC) at the Treatment Meal visit as derived from severity scores rated on a 100mm VAS and use of rescue antacid. Each subject's VAS measurements throughout the entire 4-hour and 40-minutes recording period was used to calculate an AUC for that subject using the trapezoidal rule.

3.1.1.2.3.1 Heartburn Severity AUC for Intent-to-Treat Population

Heartburn severity AUC is summarized by treatment group for Intent-to-Treat population in table below.

Summary of Heartburn Severity Area Under the Curve (AUC) in mm·Hr
Protocol RAN3016
Intent-to-Treat Population

Run-In Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	319	177.4 (5.14)	173.4	0.201	
Ranitidine 150mg	320	189.3 (4.97)	178.5	0.638	0.081
Placebo	322	186.1 (5.34)	187.6		

Copied from Table 10.
P-values were calculated using ANOVA, adjusting for investigator.

Treatment Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	319	100.7 (5.04)	81.7	0.009	
Ranitidine 150mg	320	101.3 (5.38)	71.6	0.001	0.526
Placebo	322	121.4 (5.59)	100.2		

Copied from Table 10.
P-values were calculated using ANOVA, adjusting for investigator and Run-In Meal AUC.

As seen from tables above, at the Run-In Meal visit, there were no statistically significant differences in mean heartburn severity AUC between any of the three treatment groups.

At the Treatment Meal visit, it was shown that there was a statistically significant difference in the mean heartburn severity AUC between ranitidine 150mg and placebo. There was no statistically significant difference between the ranitidine 150mg and ranitidine 75mg groups.

3.1.1.2.3.2 Heartburn Severity AUC for Efficacy Evaluable Population

The results of heartburn severity AUC for the Efficacy Evaluable population are given below.

Summary of Heartburn Severity Area Under the Curve (AUC) in mm·Hr
Protocol RAN3016
Efficacy Evaluable Population

Run-In Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	240	180.4 (5.93)	178.0	0.605	
Ranitidine 150mg	253	189.4 (5.71)	179.9	0.580	0.295
Placebo	271	185.4 (5.87)	187.0		

Copied from Table 10.2.
P-values were calculated using ANOVA, adjusting for investigator.

Treatment Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	240	97.3 (5.64)	79.6	0.018	
Ranitidine 150mg	253	98.7 (5.81)	71.3	0.025	0.870
Placebo	271	115.6 (5.72)	92.4		

Copied from Table 10.2.
P-values were calculated using ANOVA, adjusting for investigator and Run-In Meal AUC.

As seen from tables above, the results of heartburn severity AUC for the Efficacy Evaluable population were similar to those for Intent-to-Treat population.

3.1.1.2.3.3 **Three Clinical Endpoints**

These three dichotomous clinical endpoints were defined and suggested by Dr. Robie-Sue, medical officer.

Each subject's response to treatment was categorized for each of the following three dichotomous clinical endpoints:

- Reduction by 40 mm·hour or more in heartburn severity AUC from Run-In to Treatment Meal visits
- Reduction by 50% or more in heartburn severity AUC from Run-In to Treatment Meal visits
- Average Post-Treatment Meal LOCF heartburn severity scores of 17 mm or less

The number of successful outcomes for each subject on the three clinical endpoints for Intent-to-Treat is summarized below.

Summary of Number of Successes on Three Clinical Endpoints
Protocol RAN3016
Intent-to-Treat Population

	Ranitidine 75mg N=320	Ranitidine 150mg N=320	Placebo N=322
Number of Successes on the Three Clinical Endpoints			
0	93 (29%)	85 (27%)	121 (38%)
1	78 (24%)	70 (22%)	80 (25%)
2	34 (10%)	26 (8%)	24 (7%)
3	115 (36%)	139 (43%)	97 (30%)
Comparison with Placebo	0.009	<0.001	
Comparison with Ranitidine 75mg		0.180	

Copied from Table 12.
P-values were calculated using a Mantel-Haenszel test stratified by investigator

As seen from table above, the number of "successes" was statistically significantly different between subjects in the ranitidine 150mg and placebo groups. No statistically significant difference between the ranitidine 75mg and the ranitidine 150mg groups was observed.

The summary of success on each of three clinical endpoints for Intent-to-Treat population is given below.

Summary of Number of Subject with Success on Each of Three Clinical Endpoints
Protocol RAN3016
Intent-to-Treat Population

Clinical Endpoint	Ranitidine 75mg N=320	Ranitidine 150mg N=320	Placebo N=322
Heartburn severity AUC reduction by 40 mm·hour or more	191/320 (60%)	213/320 (67%)	168/322 (52%)
Comparison with Placebo	0.039	<0.001	
Comparison with Ranitidine 75mg		0.098	
Heartburn severity AUC Reduction by 50% or more	145/319 (45%)	161/320 (50%)	121/322 (38%)
Comparison with Placebo	0.029	0.002	
Comparison with Ranitidine 75mg		0.254	
Average post-treatment meal LOCF Heartburn severity score of 17mm or less	155/320 (48%)	165/320 (52%)	130/322 (40%)
Comparison with Placebo	0.020	0.006	
Comparison with Ranitidine 75mg		0.550	

Copied from Tables 13 - 15.
Correction was made in Adjustment to Clinical Report
P-values were calculated using a Mantel-Haenszel test stratified by investigator

As seen from table above, results consistently favored the ranitidine 150mg treatment group over placebo for all of three clinical endpoints. There was no statistically significant difference between the ranitidine 150mg and 75mg treatment groups.

3.1.1.2.4 **Sponsor's Analysis of Secondary Efficacy Variable**

3.1.1.2.4.1 **Reduction of Heartburn Severity**

The reduction and the percentage reduction in heartburn severity AUC from the qualifying Run-In Meal to Treatment Meal visit is summarized below.

Summary of Reduction in Heartburn Severity AUC in mm Hrs
Protocol RAN3016
Intent-to-Treat Population

Reduction in AUC

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	319	76.8 (4.96)	65.2	0.009	
Ranitidine 150mg	320	88.0 (5.36)	79.7	0.001	0.526
Placebo	322	64.8 (5.53)	50.4		

Copied from Table 16.
P-values were calculated using ANOVA, adjusting for investigator and Run-In Meal AUC.

Percentage Reduction in AUC

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	318	39.8 (2.97)	42.8	0.004	
Ranitidine 150mg	320	43.7 (2.98)	51.6	<0.001	0.619
Placebo	322	28.7 (3.32)	36.0		

Copied from Table 16.
One ranitidine 75mg subject was excluded from analysis of percentage reduction of AUC because the run-in AUC was zero.
P-values were calculated using ANOVA, adjusting for investigator and Run-In Meal AUC.

As seen from tables above, the mean reduction in heartburn severity AUC was statistically significantly greater in ranitidine 150mg group as compared to placebo. There was no statistically significant difference between the ranitidine 150mg and ranitidine 75mg treatment groups.

The mean percentage reduction in heartburn severity AUC was statistically significantly greater in ranitidine 150mg group as compared to placebo. There was no statistically significant difference between the ranitidine 150mg and 75mg treatment groups.

3.1.1.2.4.2 **Peak Heartburn Severity**

Post-meal peak heartburn severity LOCF scores by treatment group is summarized below.

Summary of Peak Heartburn Severity LOCF Score
Protocol RAN3016
Intent-to-Treat Population

Run-In Meal

Treatment	N	Mean	(SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	320	69.5	(1.09)	69.0	0.429	
Ranitidine 150mg	320	71.9	(1.02)	74.0	0.378	0.100
Placebo	322	70.9	(1.10)	71.0		

Copied from Table 17.
Correction was made in Adjustment to Clinical Report
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

Treatment Meal

Treatment	N	Mean	(SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	319	44.8	(1.56)	45.0	0.005	
Ranitidine 150mg	320	44.7	(1.68)	42.0	0.009	0.699
Placebo	322	51.5	(1.63)	51.0		

Copied from Table 17
Correction was made in Adjustment to Clinical Report.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

Reduction (%) in Peak Heartburn Severity

Treatment	N	Mean	(SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	318	35.3	(2.19)	32.9	0.004	
Ranitidine 150mg	320	37.7	(2.29)	36.5	<0.001	0.405
Placebo	322	27.1	(2.21)	20.5		

Copied from Table 17.
One ranitidine 75mg subject was excluded from analysis of percentage reduction of in peak heartburn severity because the run-in severity was zero.
Correction was made in Adjustment to Clinical Report
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

As seen from tables above, during the Treatment Meal visit, the median peak heartburn severity LOCF score was statistically significantly lower in the ranitidine 150mg group than that of the placebo group. The difference between the two ranitidine groups was not statistically significant.

The median percentage reduction in heartburn severity score LOCF scores from the Run-In to the Treatment Meal visit was statistically significantly greater in ranitidine 150mg group as compared to placebo. No statistically significant difference between two ranitidine groups was observed.

3.1.1.2.4.3 Number of Subjects with Complete Prevention

The number and percentage of subjects with complete prevention of meal-induced heartburn at Treatment Meal visit is summarized below. Only subjects with a heartburn severity score of zero (0) just prior to the meal were included in this analysis.

Summary of Complete Prevention of Heartburn
Protocol RAN3016
Intent-to-Treat Population

Treatment Meal

Treatment	Complete Prevention	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	16/263 (6%)	0.442	
Ranitidine 150mg	20/283 (7%)	0.306	0.905
Placebo	15/283 (5%)		

Copied from Table 18.
P-values were calculated using Mantel-Haenszel test stratified by investigator.
Only subjects who reported not having heartburn symptoms at the start of the meal were included in the analysis.
Correction was made in Adjustment to Clinical Report

As seen from table above, treatment groups did not differ significantly in the number of subjects achieving complete prevention during the Treatment Meal visit.

3.1.1.2.4.4 Duration after Meal without Heartburn Symptoms

The number of minutes after the meal until subjects reported LOCF heartburn symptoms by treatment group is summarized below. Only subjects who reported no heartburn symptoms at the start of the meal were included in this analysis.

Summary of Duration (Minutes) After Meal without Heartburn Symptoms
Protocol RAN3016
Intent-to-Treat Population

Run-In Meal

Treatment	N	Mean	(SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	296	9.2	(1.16)	0.0	0.349	
Ranitidine 150mg	305	8.0	(0.88)	0.0	0.850	0.449
Placebo	304	7.9	(0.87)	0.0		

Copied from Table 19.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).
Correction was made in Adjustment to Clinical Report
Only subjects who reported not having heartburn symptoms at the start of the meal were included in the analysis.

Treatment Meal

Treatment	N	Mean	(SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	263	32.5	(3.92)	7.5	0.978	
Ranitidine 150mg	283	34.0	(3.91)	7.5	0.627	0.985
Placebo	283	28.4	(3.37)	7.5		

Copied from Table 19.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).
Correction was made in Adjustment to Clinical Report
Only subjects who reported not having heartburn symptoms at the start of the meal were included in the analysis.

As seen from tables above, during the Run-In Meal visit, the median duration without any heartburn symptoms was zero minutes in all three treatment groups. During the Treatment Meal visit, the median duration without any heartburn symptoms was numerically identical in all treatment groups. There were no differences between ranitidine 150mg and placebo in duration, and therefore no additional pairwise contrasts were examined.

3.1.1.2.4.5 Largest Number of Consecutive Timepoints without Heartburn

The largest number of consecutive 15-minute post-meal evaluation timepoints (during the 40-280 minute post-meal evaluations) at which subjects had "No" LOCF heartburn symptoms, by treatment group is summarized below.

Summary of Largest Number of Consecutive Timpoints without Heartburn
Protocol RAN3016
Intent-To-Treat Population

Run-In Meal

Treatment	N	Mean	(SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	320	1.6	(0.15)	1.0	0.512	
Ranitidine 150mg	320	1.6	(0.14)	0.5	0.191	0.724
Placebo	322	1.8	(0.15)	1.0		

Copied from Table 20.
Correction was made in Adjustment to Clinical Report
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

Treatment Meal

Treatment	N	Mean	(SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	320	4.3	(0.28)	2.0	0.163	
Ranitidine 150mg	320	4.5	(0.29)	2.5	0.113	0.985
Placebo	322	3.7	(0.26)	2.0		

Copied from Table 20.
Correction was made in Adjustment to Clinical Report
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

As seen from tables above, during the Run-In visit, the median largest number of consecutive timepoints without heartburn was statistically comparable among the three treatment groups.

During the Treatment Meal visit, the median largest number of consecutive timepoints without LOCF heartburn symptoms was not statistically significantly greater in ranitidine 150mg as compared to placebo. The difference between ranitidine 75mg and ranitidine 150mg groups was not statistically significant.

3.1.1.2.4.6 **Number of Timepoints without Heartburn**

The total number of 15-minute, post-meal evaluation timepoints (during the 40-280 minute post-meal evaluations) at which subjects had "No" LOCF heartburn symptoms, by treatment group is summarized below.

Summary of Number of Timepoints Without Heartburn
Protocol RAN3016
Intent-To-Treat Population

Run-In Meal

Treatment	N	Mean	(SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	320	2.1	(0.19)	1.0	0.748	
Ranitidine 150mg	320	2.0	(0.17)	0.5	0.228	0.666
Placebo	322	2.2	(0.18)	1.0		

Copied from Table 21.
Correction was made in Adjustment to Clinical Report
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

Treatment Meal

Treatment	N	Mean	(SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	320	5.1	(0.31)	3.0	0.115	
Ranitidine 150mg	320	5.3	(0.32)	3.0	0.096	0.894
Placebo	322	4.4	(0.29)	2.0		

Copied from Table 21.
Correction was made in Adjustment to Clinical Report
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

As seen from tables above, during the Run-In visit, the median number of timepoints without LOCF heartburn symptoms was not statistically different for any of the pairwise treatment group comparisons.

During the Treatment Meal visit, the median number of timepoints without LOCF heartburn symptoms was not statistically significantly greater in ranitidine 150mg as compared to placebo. The difference between ranitidine 75mg and ranitidine 150mg groups was not statistically significant.

3.1.1.2.4.7 **Number of Subjects with Antacid Rescue Use**

The number of subjects with antacid rescue use is summarized below.

Summary of Rescue Antacid Use
Protocol RAN3016
Intent-to-Treat Population

Run-In Meal

Treatment	Rescue Antacid Use	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	82/320 (26%)	0.245	
Ranitidine 150mg	92/320 (29%)	0.030	0.363
Placebo	70/322 (22%)		

Copied from Table 22.
P-values were calculated using Mantel-Haenszel test stratified by investigator.

Treatment Meal

Treatment	Rescue Antacid Use	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	28/320 (9%)	0.305	
Ranitidine 150mg	22/320 (7%)	0.073	0.382
Placebo	36/322 (11%)		

Copied from Table 22.
P-values were calculated using Mantel-Haenszel test stratified by investigator.

As seen from tables above, rescue antacid use during the Run-In Meal was significantly greater among subjects later randomized to the ranitidine 150mg group as compared to subjects later randomized to placebo. No additional pairwise baseline imbalances were detected.

During the Treatment Meal visit, there was no statistically significant difference between the ranitidine 150mg group and the placebo group in terms of rescue antacid use.

3.1.1.2.4.8 **Subject Global Evaluation**

The results of the subject's global evaluation at the Run-In and Treatment Meal visits, by treatment group are summarized below.

Summary of Subject Global Evaluation
Protocol RAN3016
Intent-to-Treat Population

	Ranitidine 75mg N=320	Ranitidine 150mg N=320	Placebo N=322
Run-In Meal			
N	318	317	322
Subject Global Score			
0=No Effect	79 (25%)	68 (21%)	75 (23%)
1=Poor	60 (19%)	69 (22%)	64 (20%)
2=Fair	65 (20%)	70 (22%)	65 (20%)
3=Good	55 (17%)	52 (16%)	66 (20%)
4=Very Good	47 (15%)	43 (14%)	43 (13%)
5=Excellent	12 (4%)	15 (5%)	9 (3%)
Mean of subject global score	1.9	1.9	1.9
Median of subject global score	2.0	2.0	2.0
Comparison with Placebo	0.834	0.711	
Comparison with Ranitidine 75mg		0.712	
Treatment Meal			
N	317	320	321
Subject Global Score			
0=No Effect	24 (8%)	15 (5%)	35 (11%)
1=Poor	16 (5%)	30 (9%)	51 (16%)
2=Fair	62 (20%)	66 (21%)	58 (18%)
3=Good	88 (28%)	74 (23%)	82 (26%)
4=Very Good	85 (27%)	98 (31%)	71 (22%)
5=Excellent	42 (13%)	37 (15%)	24 (7%)
Mean of subject global score	3.0	3.0	2.5
Median of subject global score	3.0	3.0	3.0
Comparison with Placebo	<0.001	<0.001	
Comparison with Ranitidine 75mg		0.741	

Copied from Table 24.
Correction was made in Adjustment to Clinical Report
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

As seen from table above, during the Run-In Meal visit, subjects' median global evaluation scores were the same for all three treatment groups and there were no statistically significant differences.

During the Treatment Meal visit, the median global evaluation score was 3.0 for each of the treatment groups. Comparison of the rank differences in global assessment between treatment groups revealed that ranitidine 150mg group was statistically significantly better than the placebo group.

3.1.1.3 Reviewer's Comments and Evaluation

3.1.1.3.1 Disproportional Protocol Deviation

There was disproportional proportion of subjects who deviated from study protocol among treatment groups (p=0.0159). The ranitidine 75mg group had higher proportion of subjects who deviated from study protocol than the placebo group (25% vs. 16%; p=0.0040).

3.1.1.3.2 Multiplicity Issue

In the protocol it stated the application of this Bonferroni-Holm adjustment was performed in a hierarchical fashion. Each of the active treatments was first compared to placebo at an $\alpha/2$ (0.025) level of significance. If either of these two active treatments was statistically significantly superior to placebo, the two active treatments were compared at a 0.05 level of significance.

Per the protocol amendment, three pairwise comparisons could be performed for each parameter: ranitidine 150mg vs. placebo; ranitidine 75mg vs. placebo; and ranitidine 150mg vs. ranitidine 75mg. First, ranitidine 150mg was compared to placebo at the α=0.05 level of significance. Second, only if the first comparison was statistically significant, then ranitidine 75mg was compared to placebo at the α=0.05 level of significance. Third, if both of these two comparisons were statistically significant, the final comparison between ranitidine 150mg and ranitidine 75mg was performed at the α=0.05 level of significance.

The only comparisons of interest for this review are ranitidine 150mg versus placebo and ranitidine 150mg versus ranitidine 75mg. The p-values for ranitidine 150mg vs. placebo comparisons are shown to confirm that the testing procedure was followed.

3.1.1.3.3 LOCF Analyses

The sponsor used the LOCF (last observation carried forward) method to replace missing and non-meaning heartburn severity VAS score in both analysis of primary efficacy endpoint and analyses of secondary efficacy endpoints. It is not clear whether the LOCF analysis would provides robust results. Sensitivity analysis should be carried out.

3.1.1.3.4 Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Endpoint

3.1.1.3.4.1 Heartburn Severity AUC

For the pre-specified primary endpoint, heartburn severity AUC, it was shown that at the Treatment Meal visit, that there was a statistically significant difference in mean heartburn severity AUC between the ranitidine 150mg and placebo treatment groups for both Intent-to-Treat and efficacy evaluable populations. The treatment differences of means between ranitidine 150mg and placebo were 20.1 mm·hr and 16.9 mm·hr for Intent-to-Treat and efficacy evaluation populations, respectively.

There was no statistically significant difference between the ranitidine 150mg and ranitidine 75 groups. The treatment differences of means between ranitidine 150mg and ranitidine 75mg were 0.6 mm·hr and 1.4 mm·hr for Intent-to-Treat and efficacy evaluation populations, respectively, in favor of ranitidine 75mg group.

3.1.1.3.4.2 **Three Clinical Endpoints**

The analyses of three clinical endpoints were considered as post-hoc analyses. However, this study showed statistically significant differences between ranitidine 150mg and placebo for all three clinical endpoints. The treatment differences of between ranitidine 150mg and ranitidine 75mg ranged from 4% to 7% for all three endpoints in favor of ranitidine 150mg.

3.1.1.3.4.3 **Subgroup Analysis**

The sponsor also performed subgroup analyses of the primary efficacy endpoint by race (White vs. non-white), gender, and age (<65 vs. ≥65). The results for subgroup analyses are given below.

Treatment Meal Heartburn Severity AUC for by Subgroup
Protocol RAN3016
Intent-to-Treat Population

	Ranitidine 75mg			Ranitidine 150mg			Placebo			Ran 75mg vs Placebo	Ran 150mg vs. Placebo	Ran 75mg vs. Ran 150mg
Subgroup	N	Mean	Median	N	Mean	Median	N	Mean	Median	P-value	P-value	P-value
Race												
White	210	90.3	67.8	225	92.9	66.6	220	114.9	87.5	0.007	0.002	0.704
Non-White	109	120.6	104.3	95	121.2	103.6	102	135.4	129.3	0.814	0.319	0.439
Gender												
Male	115	90.8	69.3	111	91.9	66.6	127	107.2	76.8	0.100	0.108	0.980
Female	204	106.2	86.8	209	106.3	74.8	195	130.6	118.1	0.024	0.004	0.522
Age												
<65	306	98.6	80.1	304	103.7	73.7	304	120.3	97.4	0.010	0.007	0.927
≥65	13	148.7	115.6	16	54.8	10.9	18	139.5	133.8	0.224	0.005	0.156

Copied from Tables 10.37-10.42.
P-values were calculated using a ANOVA, adjusting for by investigator and Run-In Meal AUC.

As seen from table above, Non-white subjects tended to have higher mean heartburn severity AUC than white subjects. Female subjects had higher mean heartburn severity AUC than male subjects. Ranitidine 150mg group was more effective than placebo in white subjects and subjects age <65.

3.1.1.3.5 Reviewer's Comments on Sponsor's Analysis of Secondary Efficacy Variables

This study revealed that the ranitidine 150mg was more effective than placebo in 3 of 8 secondary efficacy endpoints: reduction of heartburn severity, peak heartburn severity, and subject global evaluation.

3.1.2 Study RAN3018

3.1.2.1 Study Design

This study was a randomized, multicenter (36 sites), double-blind, placebo-controlled, parallel evaluation of ranitidine for reduction of severity or prevention of meal-induced heartburn.

The study design of this study was similar to that for the Study RAN3016 with some exceptions listed below.

Main criteria for inclusion included: to participate in this study subject should have achieved relief of heartburn symptoms through the use of antacids during the last six months.

The primary efficacy endpoint included prevention of success - clinical endpoint in addition to heartburn severity – AUC.

The criteria of "or subjects had experienced complete prevention" was added to three clinical endpoints.

Time for the criteria for first clinical endpoint had changed from 40 minutes to 45 minutes for decreasing in AUC from the Run-In to the Treatment Meal visit.

The secondary efficacy endpoints did not include need for antacid rescue and time to antacid rescue.

OTC H_2 antagonists might be used to treat heartburn between Meal 1 (Visit 3) and Meal 2 (Visit 4).

Subjects who took rescue antacid within 90 minutes of the scheduled completion time of Meal 1 (12:30 pm) prior to reaching a discomfort level of $\geq$34mm was not disqualified after Meal 1 and prior to Meal 2 (Visit 4)

Antacid use was not assessed.

The heartburn severity score prior to meal was not assessed for protocol compliance.

Pairwise comparisons between treatment groups were done in a stepdown hierarchical manner. Since the ranitidine 150mg vs. placebo was the comparison of most interest, and

was expected to be the largest, this difference was tested at the alpha=0.05 level. If this value was less than or equal to 0.05, the other two pairwise comparisons (ranitidine 75mg vs. placebo and ranitidine 150mg vs. ranitidine 75mg) was made, each at the alpha=0.05 level.

The secondary efficacy endpoints did not include need for antacid rescue and time to antacid rescue.

3.1.2.2 Sponsor's Analysis

Three thousand one hundred seventy (3,170) subjects returned the seven day Screening diary. Nine hundred twenty-one (921) subjects successfully completed the Run-In Phase, were randomized to treatment, and entered the Treatment Phase of the study (309 ranitidine 75mg, 306 ranitidine 150mg, and 306 placebo).

Among 921 randomized subjects, 918 subjects completed the Treatment Meal visit. Three subjects prematurely discontinued from the study. Two subjects, one each in the placebo and ranitidine 75mg treatment groups, discontinued due to an adverse events. One subject in the ranitidine 150mg group discontinued due to non-compliance with the protocol.

A total of 135 subjects (51 in ranitidine 75mg, 45 in ranitidine 150mg and 39 in placebo) deviated from the study protocol and were excluded from the Efficacy Evaluable population. The three most common reasons for the exclusion of subjects from the Efficacy Evaluable population were: (1) insufficient heartburn discomfort (VAS score <34mm) within the first 90 minutes follow the Run-In Meal, (2) heartburn severity >10mm prior to Treatment Meal; and (3) failure to consume the same portions at both meals.

3.1.2.2.1 Planned Analysis

If the primary endpoint (Heartburn Severity – AUC) showed that ranitidine 150mg was significant better than placebo, further analyses were performed to investigate the clinical meaningfulness of the result. This was in response to the FDA's interest expressed during a meeting held on July 18, 1997, requesting subject success/failure rates based on dichotomous endpoints, to provide consumers with efficacy information that is easier to understand.

Three separate clinical definition of success were explored, each related to the primary endpoint of heartburn AUC. The first clinical endpoint of interest defined subjects as being a treatment success if they had an average post-meal VAS score at Meal 2 of 17 mm or less. The second defined a subject as being a treatment success if they showed a decrease in AUC from Meal 1 to Meal 2 of 20 or more mm·hr or experienced complete prevention. The third clinical endpoint defined subjects as treatment success if their Meal 2 AUC is 50% or less than their Meal 1 AUC.

A composite score was created, as the number of these three clinical definitions on which a subject was declared successful. This composite score, also known as the O'Brien method, acted as an overall test of clinical difference between the treatments. If ranitidine 150mg was significantly different from placebo for this overall composite score, then each clinical success component was analyzed separately to assess the clinical significance.

3.1.2.2.2 Treatment Group Comparability

A summary of the number of patients by baseline characteristics by treatment group is given in Appendix Table 2.

As seen from Appendix Table 2, the treatment groups appeared similar with regard to all baseline characteristics.

3.1.2.2.3 Sponsor's Analysis of Primary Efficacy Variable

The primary efficacy endpoint was the heartburn severity area under the curve (AUC) at the Treatment Meal visit as derived from severity scores rated on a 100mm VAS and use of rescue antacid. Each subject's VAS measurements throughout the entire 4-hour and 40-minutes recording period was used to calculate an AUC for that subject using the trapezoidal rule.

3.1.2.2.3.1 Heartburn Severity AUC for Intent-to-Treat Population

Heartburn severity AUC is summarized by treatment group for Intent-to-Treat population in table below.

Summary of Heartburn Severity Area Under the Curve (AUC) in mmHr
Protocol RAN3018
Intent-to-Treat Population

Run-In Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	309	176.0 (5.29)	166.0	0.821	
Ranitidine 150mg	306	178.3 (5.32)	167.9	0.683	0.855
Placebo	306	174.4 (4.93)	164.8		

Copied from Table 10.
P-values were calculated using ANOVA, adjusting for investigator.

Treatment Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	309	88.6 (4.97)	63.3	0.114	
Ranitidine 150mg	306	94.6 (5.91)	54.5	0.372	0.491
Placebo	306	98.8 (4.83)	79.8		

Copied from Table 10.
P-values were calculated using ANOVA, adjusting for investigator and Run-In Meal AUC.

As seen from tables above, there were no statistically significant differences in mean heartburn severity AUC between any of the three treatment groups during the Run-In Meal or Treatment Meal visit.

3.1.2.2.3.2 Heartburn Severity AUC for Efficacy Evaluable Population

The results of heartburn severity AUC for the Efficacy Evaluable population are given below.

Summary of Heartburn Severity Area under the Curve (AUC) in mmHr
Protocol RAN3018
Efficacy Evaluable Population

Run-In Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	258	183.4 (5.88)	173.5	0.328	
Ranitidine 150mg	261	180.6 (5.84)	168.4	0.755	0.507
Placebo	267	176.2 (5.33)	169.1		

Copied from Table 10.2.
P-values were calculated using ANOVA, adjusting for investigator.

Treatment Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	258	89.6 (5.50)	63.7	0.342	
Ranitidine 150mg	261	90.7 (6.17)	51.0	0.301	0.938
Placebo	267	97.6 (5.01)	82.2		

Copied from Table 10.2.
P-values were calculated using ANOVA, adjusting for investigator and Run-In Meal AUC.

As seen from tables above, the results of heartburn severity AUC for the Efficacy Evaluable population were similar to those for Intent-to-Treat population

3.1.2.2.3.3 Three Clinical Endpoints

Each subject's response to treatment was categorized for each of the following three dichotomous clinical endpoints:

- Reduction by 45 mm·hour or more in heartburn severity AUC from Run-In to

Treatment Meal visits

- Reduction by 50% or more in heartburn severity AUC from Run-In to Treatment Meal visits
- Average Post-Treatment Meal LOCF heartburn severity scores of 17 mm or less

The summary of success on each of three clinical endpoints for Intent-to-Treat population is given below.

Summary of Number of Subject with Success on Each of Three Clinical Endpoints
Protocol RAN3018
Intent-to-Treat Population

Clinical Endpoint	Ranitidine 75mg N=309	Ranitidine 150mg N=306	Placebo N=306
Heartburn severity AUC reduction by 45 mm·hour or more	192/309 (62%)	198/306 (65%)	196/306 (64%)
Comparison with Placebo	0.471	0.807	
Comparison with Ranitidine 75mg		0.512	
Heartburn severity AUC Reduction by 50% or more	165/309 (53%)	173/306 (57%)	145/306 (47%)
Comparison with Placebo	0.202	0.016	
Comparison with Ranitidine 75mg		0.455	
Average post-treatment meal LOCF Heartburn severity score of 17mm or less	175/309 (57%)	176/306 (58%)	148/306 (48%)
Comparison with Placebo	0.039	0.017	
Comparison with Ranitidine 75mg		0.801	

Copied from Tables 12 - 14.
Correction was made in Adjustment to Clinical Report.
P-values were calculated using a Mantel-Haenszel test stratified by investigator

As seen from table above, there was no treatment difference between ranitidine 150mg and placebo for the clinical endpoint of reduction in AUC by 45 mm·hour or more.

The percentage of subjects who experienced AUC reduction by 50% or more was statistically significant greater for the ranitidine 150mg subjects as compared to placebo subjects. No statistically significant difference between two ranitidine groups was found.

For average post-treatment meal LOCF heartburn severity ≤17mm, ranitidine 150mg group was statistically significantly superior to the placebo group. No statistically significant difference between two ranitidine groups was found.

3.1.2.2.4 Sponsor's Analysis of Secondary Efficacy Variable

3.1.2.2.4.1 Reduction of Heartburn Severity

The reduction and the percentage reduction in heartburn severity AUC from the qualifying Run-In Meal to Treatment Meal visit is summarized below.

Summary of Reduction in Heartburn Severity AUC in mm Hrs
Protocol RAN3018
Intent-to-Treat Population

Reduction in AUC

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	309	87.4 (5.56)	73.9	0.114	
Ranitidine 150mg	306	83.7 (5.64)	73.3	0.372	0.491
Placebo	306	75.5 (5.13)	67.7		

Copied from Table 15.
P-values were calculated using ANOVA, adjusting for investigator and Run-In Meal AUC.

Percentage Reduction in AUC

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	309	43.4 (3.20)	54.6	0.389	
Ranitidine 150mg	306	45.4 (3.08)	60.1	0.174	0.616
Placebo	306	39.2 (3.05)	46.9		

Copied from Table 15.
One ranitidine 75mg subject was excluded from analysis of percentage reduction of AUC because the run-in AUC was zero.
P-values were calculated using ANOVA, adjusting for investigator and Run-In Meal AUC.

As seen from tables above, no treatment group mean differences were detected for either the reduction or percentage reduction in AUC.

3.1.2.2.4.2 Peak Heartburn Severity

Post-meal peak heartburn severity LOCF scores by treatment group is summarized below.

Summary of Peak Heartburn Severity LOCF Score
Protocol RAN3018
Intent-to-Treat Population

Run-In Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	309	71.0 (1.12)	72.0	0.912	
Ranitidine 150mg	306	70.5 (1.14)	71.0	0.639	0.905
Placebo	306	71.1 (1.09)	71.0		

Copied from Table 16.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

Treatment Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	309	43.4 (1.60)	43.0	0.068	
Ranitidine 150mg	306	42.4 (1.80)	37.0	0.091	0.399
Placebo	306	46.8 (1.61)	47.5		

Copied from Table 16
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

Reduction (%) in Peak Heartburn Severity

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	309	37.4 (2.30)	38.1	0.125	
Ranitidine 150mg	306	39.7 (2.47)	40.3	0.161	0.576
Placebo	306	32.8 (2.29)	29.8		

Copied from Table 16.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

As seen from tables above, no treatment group differences were observed for either the Run-In or the Treatment Meal visit median peak heartburn severity score. Neither were treatment group differences detected for the median percent reduction in peak heartburn severity from Run-In to Treatment Meal visit.

3.1.2.2.4.3 Number of Subjects with Complete Prevention

The number and percentage of subjects with complete prevention of meal-induced heartburn at Treatment Meal visit is summarized below. Only subjects with a heartburn severity score of zero (0) just prior to the meal were included in this analysis.

Summary of Complete Prevention of Heartburn
Protocol RAN3018
Intent-to-Treat Population

Treatment Meal

Treatment	Complete Prevention	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	24/275 (9%)	0.631	
Ranitidine 150mg	28/277 (10%)	0.328	0.519
Placebo	20/270 (7%)		

Copied from Table 17.
P-values were calculated using Mantel-Haenszel test stratified by investigator.
Only subjects who reported not having heartburn symptoms at the start of the meal were included in the analysis.

As seen from table above, treatment groups did not differ significantly in the number of subjects achieving complete prevention during the Treatment Meal visit.

3.1.2.2.4.4 Duration after Meal without Heartburn Symptoms

The number of minutes after the meal until subjects reported LOCF heartburn symptoms by treatment group is summarized below. Only subjects who reported no heartburn symptoms at the start of the meal were included in this analysis.

Summary of Duration (Minutes) After Meal without Heartburn Symptoms
Protocol RAN3018
Intent-to-Treat Population

Run-In Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	287	8.0 (0.85)	0.0	0.137	
Ranitidine 150mg	300	8.1 (0.87)	0.0	0.256	0.703
Placebo	284	5.8 (0.69)	0.0		

Copied from Table 18.
Correction was made in Adjustment to Clinical Report.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).
Only subjects who reported not having heartburn symptoms at the start of the meal were included in the analysis.

Treatment Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	275	40.2 (4.29)	7.5	0.722	
Ranitidine 150mg	277	41.6 (4.49)	7.5	0.695	0.593
Placebo	270	36.3 (4.07)	7.5		

Copied from Table 18.
Correction was made in Adjustment to Clinical Report.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).
Only subjects who reported not having heartburn symptoms at the start of the meal were included in the analysis.

As seen from tables above, during the Run-In Meal visit, the median duration without any heartburn symptoms was zero minutes in all three treatment groups. During the Treatment Meal visit, the median duration without any heartburn symptoms was numerically identical in all treatment groups. There were no difference between ranitidine 150mg and placebo in duration, and therefore no additional pairwise contrasts were examined.

3.1.2.2.4.5 Largest Number of Consecutive Timepoints without Heartburn

The largest number of consecutive 15-minute post-meal evaluation timepoints (during the 40-280 minute post-meal evaluations) at which subjects had "No" LOCF heartburn symptoms, by treatment group is summarized below.

Summary of Largest Number of Consecutive Timpoints without Heartburn
Protocol RAN3018
Intent-To-Treat Population

Run-In Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	309	2.0 (0.15)	1.0	0.307	
Ranitidine 150mg	306	1.9 (0.16)	1.0	0.464	0.695
Placebo	306	1.9 (0.16)	1.0		

Copied from Table 19.
Correction was made in Adjustment to Clinical Report.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

Treatment Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	309	5.2 (0.30)	4.0	0.148	
Ranitidine 150mg	306	5.5 (0.32)	3.0	0.032	0.583
Placebo	306	4.4 (0.29)	3.0		

Copied from Table 19.
Correction was made in Adjustment to Clinical Report.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

As seen from tables above, during the Run-In visit, the median largest number of consecutive timepoints without heartburn was statistically comparable among the three treatment groups.

During the Treatment Meal visit, the median largest number of consecutive timepoints without LOCF heartburn symptoms was statistically significantly greater in the ranitidine 150mg as compared to placebo.

3.1.2.2.4.6 **Number of Timepoints without Heartburn**

The total number of 15-minute, post-meal evaluation timepoints (during the 40-280 minute post-meal evaluations) at which subjects had "No" LOCF heartburn symptoms, by treatment group is summarized below.

Summary of Number of Timepoints without Heartburn
Protocol RAN3018
Intent-To-Treat Population

Run-In Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	309	2.5 (0.19)	1.0	0.329	
Ranitidine 150mg	306	2.2 (0.18)	1.0	0.607	0.437
Placebo	306	2.2 (0.19)	1.0		

Copied from Table 20.
Correction was made in Adjustment to Clinical Report.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

Treatment Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	309	6.1 (0.33)	3.0	0.195	
Ranitidine 150mg	306	6.4 (0.35)	3.0	0.038	0.480
Placebo	306	5.2 (0.31)	2.0		

Copied from Table 20.
Correction was made in Adjustment to Clinical Report.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

As seen from table above, during the Run-In visit, the median number of timepoints without LOCF heartburn symptoms was not statistically different for any of the pairwise treatment group comparisons.

During the Treatment Meal visit, the median number of timepoints without LOCF heartburn symptoms was statistically significantly greater in ranitidine 150mg as compared to placebo. The difference between ranitidine 75mg and placebo was not statistically significant.

3.1.2.2.4.7 **Subject Global Evaluation**

The results of the subject's global evaluation at the Run-In and Treatment Meal visits, by treatment group are summarized below.

Summary of Subject Global Evaluation
Protocol RAN3018
Intent-to-Treat Population

	Ranitidine 75mg N=309	Ranitidine 150mg N=306	Placebo N=306
Run-In Meal			
N	307	303	305
Subject Global Score			
0=No Effect	62 (20%)	80 (26%)	73 (24%)
1=Poor	72 (23%)	59 (19%)	58 (19%)
2=Fair	71 (23%)	71 (23%)	81 (27%)
3=Good	54 (18%)	49 (16%)	47 (15%)
4=Very Good	36 (12%)	33 (11%)	33 (11%)
5=Excellent	12 (4%)	11 (4%)	13 (4%)
Mean of subject global score	1.9	1.8	1.8
Median of subject global score	2.0	2.0	2.0
Comparison with Placebo	0.320	0.739	
Comparison with Ranitidine 75mg		0.197	
Treatment Meal			
N	306	300	303
Subject Global Score			
0=No Effect	17 (6%)	18 (6%)	23 (8%)
1=Poor	29 (9%)	28 (9%)	45 (15%)
2=Fair	70 (23%)	44 (15%)	73 (24%)
3=Good	68 (22%)	65 (22%)	55 (18%)
4=Very Good	84 (27%)	91 (30%)	70 (23%)
5=Excellent	38 (12%)	54 (18%)	37 (12%)
Mean of subject global score	2.9	3.2	2.7
Median of subject global score	3.0	3.0	3.0
Comparison with Placebo	0.016	<0.001	
Comparison with Ranitidine 75mg		0.035	

Copied from Table 21.
Correction was made in Adjustment to Clinical Report.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

As seen from table above, during the Run-In Meal visit, subjects' median global evaluation scores were the same for all three treatment groups and there were no statistically significant differences.

During the Treatment Meal visit, the median global evaluation score was 3.0 for each of the treatment groups. Comparison of the rank differences in global assessment between treatment groups revealed that ranitidine 150 mg group was statistically significantly better than the placebo group. Furthermore, ranitidine 150mg group was significantly superior to ranitidine 75mg.

3.1.2.3 **Reviewer's Comments and Evaluation**

3.1.2.3.1 **Multiplicity Issue**

In the protocol it was pre-specified to use a stepdown hierarchical method for multiplicity. Pairwise comparisons between treatment groups were done in a stepdown hierarchical manner. Since the ranitidine 150mg vs. placebo was the comparison of most interest, and was expected to be the largest, this difference was tested at the alpha=0.05 level. If this value was less than or equal to 0.05, the other two pairwise comparisons (ranitidine 75mg vs. placebo and ranitidine 150mg vs. ranitidine 75mg) was made, each at the alpha=0.05 level.

The only comparisons of interest for this review are ranitidine 150mg versus placebo and ranitidine 150mg versus ranitidine 75mg. The p-values for ranitidine 150mg vs. placebo comparisons are shown to confirm that the testing procedure was followed.

3.1.2.3.2 **LOCF Analyses**

The comments stated for Protocol RAN3016 also apply to this study.

3.1.2.3.3 **Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Endpoint**

3.1.2.3.3.1 **Heartburn Severity AUC**

For the pre-specified primary endpoint, heartburn severity AUC, it was shown that at the Treatment Meal visit, that there was not statistically significant difference in mean heartburn severity AUC between the ranitidine 150mg and placebo treatment groups for both Intent-to-Treat and efficacy evaluable populations. The treatment differences of means between ranitidine 150mg and placebo were 4.2 mm·hr and 6.9 mm·hr for Intent-to-Treat and efficacy evaluation populations, respectively.

There was no statistically significant difference between the ranitidine 150mg and ranitidine 75mg groups. The treatment differences of means between ranitidine 150mg and ranitidine 75mg were 6.0 mm·hr and 1.1 mm·hr for Intent-to-Treat and efficacy evaluation populations, respectively, in favor of ranitidine 75mg group.

3.1.2.3.3.2 **Three Clinical Endpoints**

The analyses of three clinical endpoints were considered as post-hoc analyses.

In the protocol, the second of three clinical endpoints was defined a subject as being a treatment success if they showed a decrease in AUC from Meal 1 to Meal 2 of 20 or more mm·hr or experienced complete prevention. But, in the sponsor's analysis of this endpoint, a subject as being a treatment success if they had reduction by 45 mm·hour or more in heartburn severity AUC from Run-In to Treatment Meal visits.

It is unclear whether the number of 20 mm·hr used for defined as a success in the protocol was a typo. Even the corrected number was 40 mm·hr as used for protocol RAN3016, the sponsor's analysis of this endpoint should be considered as hypothesis generating.

3.1.2.3.3.3 Subgroup Analysis

The sponsor also performed subgroup analyses of the primary efficacy endpoint by race (White vs. non-white), gender, and age (<65 vs. ≥65). The results for subgroup analyses are given below.

Treatment Meal Heartburn Severity AUC for by Subgroup
Protocol RAN3018
Intent-to-Treat Population

	Ranitidine 75mg			Ranitidine 150mg			Placebo			Ran 75mg vs Placebo	Ran 150mg vs. Placebo	Ran 75mg vs. Ran 150mg
Subgroup	N	Mean	Median	N	Mean	Median	N	Mean	Median	P-value	P-value	P-value
Race												
White	241	77.0	51.1	235	85.4	45.5	224	90.4	66.1	0.024	0.330	0.194
Non-white	68	129.5	91.1	71	124.9	120.4	82	121.8	115.7	0.127	0.947	0.152
Gender												
Male	110	75.2	47.8	114	66.4	32.5	99	98.5	82.2	0.012	0.011	0.960
Female	199	96.0	80.8	192	111.3	74.3	207	99.0	79.3	0.560	0.506	0.219
Age												
<65	292	88.1	62.8	285	92.6	54.0	293	98.7	79.3	0.085	0.293	0.509
≥65	17	97.1	93.8	21	121.1	110.5	13	102.2	83.2	0.169	0.346	0.725

Copied from Tables 10.39-10.44.
P-values were calculated using a ANOVA, adjusting for by investigator and Run-In Meal AUC.

As seen from table above, non-white subjects tended to have higher mean heartburn severity AUC than white subjects. Female subjects in both ranitidine groups had higher mean heartburn severity AUC than male subjects. Superiority of ranitidine 150mg versus placebo was not consistent across gender.

3.1.2.3.4 Reviewer's Comments on Sponsor's Analysis of Secondary Efficacy Variables

This study revealed that the ranitidine 150mg was more effective than placebo in only 1 of 7 secondary efficacy endpoints: subject global evaluation. It failed to achieve statistical significance level of 0.025 in these two secondary efficacy endpoints: largest number of consecutive timepoints without heartburn and number of timepoint without heartburn.

3.1.3 Study RAN4006

3.1.3.1 Study Design

This study was a randomized, multicenter (23 sites), double-blind, placebo-controlled, parallel evaluation of ranitidine for reduction of severity or prevention of meal-induced heartburn.

The study design of this study was similar to that for the Study RAN3016 with some exceptions listed below.

Subjects who met the minimum requirements at the Run-In Meal visit were scheduled to return for the Treatment Meal visit within 4 to 16 days after the Run-In Meal visit.

Subject returned to clinic between 8 and 26 days from their prescreening visit for diary card review.

At the conclusion of the Treatment Meal evaluation period, subjects were not given a diary card to record any new post-Treatment Meal heartburn episodes, the cause, time and day of the week of episode, level of discomfort and if they treated the episode. .

Exclusion criteria did not include:

a.The subject had ever taken omeprazole or lansoprazole.
b.The subject was a current methadone user.
c.The subject had history of allergies to any portion of the test meal.

Secondary efficacy endpoints did not include the longest duration of no heartburn, total duration of no heartburn, complete prevention, extended reduction of severity or prevention of heartburn symptoms, and nocturnal heartburn symptoms.

For duration with symptoms, the longest duration of complete prevention was assessed.

The global question: "From the time you took your medication until now, how would you rate the discomfort level you experienced due to each of the following 11 symptoms?" was not included.

The pairwise comparisons were performed in a hierarchical fashion. Each of the active treatments with was first compared to placebo at an $\alpha/2$ (0.025) level of significance (Boneferrroni-Holm adjustment). If both active treatments were statistically significantly superior to placebo, the two active treatments were compared at a 0.05 level of significance.

In the sample size determination, assuming a standard deviation of 60mm, sample size of 192 subjects per arm was needed.

3.1.3.2 Sponsor's Analysis

Two thousand nine hundred forty-nine (2,949) subjects returned the diary. Six hundred one (601) subjects successfully completed the Run-In Phase, were randomized to treatment, and entered the Treatment Phase of the study (204 ranitidine 75mg, 198 ranitidine 150mg, and 199 placebo).

All of these subjects completed the Treatment Meal and there were no premature discontinuations from the study.

A total of 115 subjects (51 in ranitidine 75mg, 35 in ranitidine 150mg and 29 in placebo) deviated from the study protocol and were excluded from the Efficacy Evaluable population. The three most common reasons responsible for exclusion of subjects from the Efficacy Evaluable population were: (1) insufficient heartburn discomfort (VAS core <34mm) within the first 90 minutes following the Run-In Meal; (2) failure to consume the same number of portions at both meals; and (3) having a heartburn severity VAS score >10mm just prior to eating the Run-In Meal.

3.1.3.2.1 Planned Analysis

Additional analyses were performed to supplement the planned analyses. These data-driven analyses were performed after the study blind was broken and were discussed below.

One revision to the calculation of LOCF heartburn severity was necessary. There were a few instances in which subjects identified themselves as having "No" heartburn symptoms, but also rated the severity of those symptoms as being greater than zero. Because it could not be determined whether the symptom indicator or severity score was incorrect, neither value was changed. The original protocol did not anticipate this type of data anomaly when it instructed that a zero be imputed into all severity scores that corresponding to the indication of "No" symptoms.

It was determined that using the LOCF methodology for only the severity scores created an inconsistency between those variables derived from severity scores and those derived from symptom indicators. It was therefore decided that a similar LOCF methodology should be applied to the heartburn symptom indicators as well. The methodology was as follows. First, all symptom indicators following the use of rescue antacid were assigned a value of "Yes." This replacement was necessary because symptom indicators following the use of antacid were not directly interpretable. Second, if the heartburn symptom indicator was missing, but the LOCF severity score was non-missing, the symptom indicator was adjusted to correspond to the severity score (e.g., symptom indicators would be set to "Yes" if their corresponding LOCF severity scores were greater than zero). Third, symptom indicators that remained missing after this imputation received the value of the most immediately preceding, non-missing symptom indicator. If, however, the 40-minutes observation (the first post-meal observation) was missing, the indicator at time zero was not imputed into this observation.

In response to the imbalance, the decision was made by the sponsor to include all variables that could impact the response to treatment in the analysis of primary efficacy parameter.

Based on discussion with the FDA (meeting of 18 July, 1997), additional endpoints that provide consumer-meaningful outcome measures were included in the protocol amendment. These endpoints were similar to those generated in clinical studies with other OTC H_2-receptor antagonists. These clinical endpoints categorize study treatment effect on a per subject basis of either success or failure are all related to the primary endpoint of heartburn severity as measured by the AUC.

Each subject's response to treatment was categorized for each of the following three dichotomous clinical endpoints:

- Reduction by 40 mm·hour or more in heartburn severity AUC from Run-In to Treatment Meal visits
- Reduction by 50% or more in heartburn severity AUC from Run-In to Treatment Meal visits
- Average Post-Treatment Meal LOCF heartburn severity scores of 17 mm or less

Furthermore, for each clinical endpoint, a subject who achieved complete prevention of heartburn severity at all post-Treatment Meal visit evaluations was classified as a "success', whereas a subject who used rescue antacid during the Treatment Meal visit was classified as a "failure." In addition, for the dichotomous endpoints, a 10% point difference between an active treatment and placebo was declared as a clinically meaningful difference.

A composite score was calculated as the sum of three clinical definitions on which a subject was declared a success. If ranitidine 150mg was significantly different from placebo at this overall level, each component was analyzed separately for clarification of clinical effect.

The "Number of Subjects with Complete Prevention" analysis was inadvertently omitted by sponsor from this study protocol but had been used as a secondary efficacy endpoint in previous meal-induced heartburn studies. Two other analyses related to the complete prevention endpoint ("Largest Number of Consecutive Timepoints without Heartburn" and "Number of Timepoints without Heartburn") were included.

Number of Subjects with Complete Prevention

Complete prevention of heartburn was defined as the indication of "No" symptoms at each post-meal assessment during the evaluation period. The LOCF symptom indicators were utilized to determine complete prevention. Therefore, individuals who used rescue antacid were necessarily identified as treatment failures. Furthermore, only subjects who reported no heartburn symptoms at the start of the meal were included in this analysis.

The complete prevention endpoint was compared across treatment groups using the Mantel-Haenszel test stratified by investigator.

Largest Number of Consecutive Timepoint without Heartburn

The largest number of consecutive 15-minute post-meal timepoints (40 minutes post-meal to 280 minutes; for a total of 17 timepoints) at which the LOCF heartburn symptom indicator had a value of "No' was calculated for each subject. The median number of timepoints was compared for treatment group difference using Wilcoxon rank-sum test stratified by investigator (van Elteren test).

Number of Timepoints without Heartburn Symptoms

The total number of 15-minute post-meal timepoints (40 minute post-meal to 280 minutes; for a total of 17 timepoints) at which the LOCF heartburn symptom indicator had a value of "No" was calculated for each subject. The median number of timepoints was compared for treatment group difference using Wilcoxon rank-sum test stratified by investigator (van Elteren test).

Duration without Heartburn Symptoms

The original definition of this endpoint was adjusted to account for the use of antacid rescue. It was conceivable that subjects could have used rescue antacid at any time during the study. If the first use of rescue antacid occurred prior to the first indication of heartburn symptoms, the time of antacid use was identified to be the time of first symptom. .Furthermore, because antacid rescue might have occurred during the meal itself, the duration without heartburn symptoms was calculated from dosing rather than from end of meal. Consequently, duration without heartburn symptoms was calculated by counting the number of minutes from dosing until the first of either 1) a LOCF symptom value of "Yes" or 2) the use of rescue antacid.

3.1.3.2.2 Treatment Group Comparability

A summary of the number of patients by baseline characteristics by treatment group is given in Appendix Table 3.

As seen from Appendix Table 3, the treatment groups appeared similar with regard to all baseline characteristics.

3.1.3.2.3 Sponsor's Analysis of Primary Efficacy Variable

The primary efficacy endpoint was the heartburn severity area under the curve (AUC) at the Treatment Meal visit as derived from severity scores rated on a 100mm VAS and use of rescue antacid. Each subject's VAS measurements throughout the entire 4-hour and 40-minutes recording period was used to calculate an AUC for that subject using the trapezoidal rule.

Three subjects randomized to Ranitidine 75mg were excluded from analyses of AUC because their AUC could not be calculated. One subject had no VAS score at 40 minutes after dosing for the run-in meal; two subjects took rescue antacid less than 40 minutes after dosing for the treatment meal.

3.1.3.2.3.1 Heartburn Severity AUC for All Subjects Population

Heartburn severity AUC is summarized by treatment group for all subjects population in table below.

Summary of Heartburn Severity Area under the Curve (AUC) in mm·Hr
Protocol RAN4006
All Subjects Population

Run-In Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	201	157.2 (5.72)	147.0	0.780	
Ranitidine 150mg	198	174.0 (6.28)	168.5	0.093	0.050
Placebo	199	159.8 (6.08)	149.7		

Copied from Table 10.
P-values were calculated using ANOVA, adjusting for investigator.

Treatment Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	201	75.9 (5.74)	42.2	0.259	
Ranitidine 150mg	198	63.8 (5.24)	36.6	0.006	0.102
Placebo	199	85.0 (5.81)	62.3		

Copied from Table 10.
P-values were calculated using ANOVA, adjusting for investigator .

As seen from tables above, at the Run-In Meal visit, there was a statistically significant difference in mean heartburn severity AUC in subjects later randomized to ranitidine 150mg compared to subjects later randomized to ranitidine 75mg. Similarly, the mean AUC for the ranitidine 150mg group was numerically higher than for subjects later randomized to placebo.

At the Treatment Meal visit, it was shown that there were a statistically significant difference in mean heartburn severity AUC between the ranitidine 150mg and placebo treatment groups.

3.1.3.2.3.2 Heartburn Severity AUC for Efficacy Evaluable Population

The results of heartburn severity AUC for the Efficacy Evaluable population are given below.

Summary of Heartburn Severity Area under the Curve (AUC) in mm·Hr
Protocol RAN4006
Efficacy Evaluable Population

Run-In Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	152	162.2 (6.81)	153.1	0.805	
Ranitidine 150mg	163	179.9 (6.96)	179.7	0.156	0.105
Placebo	170	166.0 (6.85)	163.5		

Copied from Table 10.2.
P-values were calculated using ANOVA, adjusting for investigator.

Treatment Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	152	76.3 (6.69)	41.9	0.233	
Ranitidine 150mg	163	70.8 (6.01)	43.7	0.070	0.563
Placebo	170	87.1 (6.33)	67.3		

Copied from Table 10.2.
P-values were calculated using ANOVA, adjusting for investigator.

As seen from tables above, at the Run-In Meal visit, mean heartburn severity AUC's of the treatment groups was not significantly different. At the Treatment Meal visit, mean heartburn severity AUC of the ranitidine 150mg group was numerically lower than that of placebo.

3.1.3.2.3.3 **Three Clinical Endpoints**

Each subject's response to treatment was categorized for each of the following three dichotomous clinical endpoints:

- Reduction by 40 mm·hour or more in heartburn severity AUC from Run-In to Treatment Meal visits
- Reduction by 50% or more in heartburn severity AUC from Run-In to Treatment Meal visits
- Average Post-Treatment Meal LOCF heartburn severity scores of 17 mm or less

The number of successful outcomes for each subject on the three clinical endpoints for Intent-to-Treat is summarized below.

Summary of Number of Successes on Three Clinical Endpoints
Protocol RAN4006
Intent-to-Treat Population

	Ranitidine 75mg N=204	Ranitidine 150mg N=198	Placebo N=199
Number of Successes on the Three Clinical Endpoints			
0	51 (25%)	35 (18%)	66 (33%)
1	34 (17%)	28 (14%)	28 (14%)
2	22 (11%)	23 (12%)	18 (9%)
3	97 (48%)	112 (57%)	87 (44%)
Comparison with Placebo	0.199	<0.001	
Comparison with Ranitidine 75mg		0.031	

Copied from Table 12.
P-values were calculated using a Mantel-Haenszel test stratified by investigator

As seen from table above, the number of "successes" was statistically significantly different between subjects in the ranitidine 150mg and placebo groups.

The summary of success on each of three clinical endpoints for Intent-to-Treat population is given below.

Summary of Number of Subject with Success on Each of Three Clinical Endpoints
Protocol RAN4006
Intent-to-Treat Population

Clinical Endpoint	Ranitidine 75mg N=204	Ranitidine 150mg N=198	Placebo N=199
Heartburn severity AUC reduction by 40 mm·hour or more	133/204 (65%)	146/198 (74%)	112/199 (56%)
Comparison with Placebo	0.082	<0.001	
Comparison with Ranitidine 75mg		0.062	
Heartburn severity AUC Reduction by 50% or more	117/204 (57%)	131/198 (66%)	105/199 (53%)
Comparison with Placebo	0.395	0.007	
Comparison with Ranitidine 75mg		0.077	
Average post-treatment meal LOCF Heartburn severity score of 17mm or less	119/204 (58%)	133/198 (67%)	108/199 (54%)
Comparison with Placebo	0.438	0.008	
Comparison with Ranitidine 75mg		0.054	

Copied from Tables 13 - 15.
P-values were calculated using a Mantel-Haenszel test stratified by investigator

As seen from table above, results consistently favored the ranitidine 150mg treatment group over placebo for all of three clinical endpoints.

3.1.3.2.4 Sponsor's Analysis of Secondary Efficacy Variable

3.1.3.2.4.1 Reduction of Heartburn Severity

The reduction and the percentage reduction in heartburn severity AUC from the qualifying Run-In Meal to Treatment Meal visit is summarized below.

Summary of Reduction in Heartburn Severity AUC in mm Hrs
Protocol RAN4006
All Subjects Population

Reduction in AUC

Treatment	N	Mean	(SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	201	81.3	(5.54)	76.3	0.469	
Ranitidine 150mg	198	110.2	(6.81)	102.1	<0.001	0.001
Placebo	199	74.8	(6.63)	65.7		

Copied from Table 16.
P-values were calculated using ANOVA, adjusting for investigator.

Percentage Reduction in AUC

Treatment	N	Mean	(SD)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	200	50.8	(3.55)	67.8	0.064	
Ranitidine 150mg	198	57.8	(4.13)	75.9	0.004	0.293
Placebo	199	39.0	(5.44)	59.1		

Copied from Table 16.
P-values were calculated using ANOVA, adjusting for investigator.

As seen from tables above, the mean reduction in heartburn severity AUC was statistically significantly greater in the ranitidine 150mg group as compared to placebo. Ranitidine 150 mg was statistically significant better than ranitidine 75 mg.

The mean percentage reduction in heartburn severity AUC was statistically significantly greater in the ranitidine 150mg group as compared to placebo.

3.1.3.2.4.2 Peak Heartburn Severity

Post-meal peak heartburn severity LOCF scores by treatment group is summarized below.

Summary of Peak Heartburn Severity LOCF Score
Protocol RAN4006
All Subjects Population

Run-In Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	204	65.9 (1.35)	64.0	0.443	
Ranitidine 150mg	198	67.9 (1.35)	68.5	0.061	0.418
Placebo	199	64.6 (1.37)	63.0		

Copied from Table 17.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

Treatment Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	202	36.6 (1.92)	34.0	0.237	
Ranitidine 150mg	198	33.0 (1.89)	26.5	0.015	0.064
Placebo	199	39.8 (1.98)	40.0		

Copied from Table 17
Correction was made in Adjustment to Clinical Report.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

Reduction (%) in Peak Heartburn Severity

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	201	44.1 (2.79)	47.4	0.171	
Ranitidine 150mg	198	50.6 (2.74)	57.0	0.003	0.098
Placebo	199	37.9 (2.99)	39.2		

Copied from Table 17.
Correction was made in Adjustment to Clinical Report.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

As seen from tables above, at the Run-In Meal visit, peak heartburn severity LOCF scores post-meal was not statistically significant different between the treatment groups. The median severity score of the ranitidine 150mg group was, however, numerically greater than the placebo.

During the Treatment Meal visit, the median peak heartburn severity LOCF score of the ranitidine 150mg group was statistically significantly lower in than that of the placebo group.

The median percentage reduction in heartburn severity score LOCF scores from the Run-In to the Treatment Meal visit was statistically significantly greater in the ranitidine 150mg group as compared to placebo.

3.1.3.2.4.3 Number of Subjects with Complete Prevention

The number and percentage of subjects with complete prevention of meal-induced heartburn at Treatment Meal visit is summarized below. Only subjects with a heartburn severity score of zero (0) just prior to the meal were included in this analysis.

Summary of Complete Prevention of Heartburn
Protocol RAN4006
All Subjects Population

Treatment Meal

Treatment	Complete Prevention	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	20/177 (11%)	0.449	
Ranitidine 150mg	22/181 (12%)	0.428	0.885
Placebo	17/188 (9%)		

Copied from Table 18.
Correction was made in Adjustment to Clinical Report.
P-values were calculated using Mantel-Haenszel test stratified by investigator.
Only subjects who reported not having heartburn symptoms at the start of the meal were included in the analysis.

As seen from table above, treatment groups did not differ significantly in the number of subjects achieving complete prevention during the Treatment Meal visit.

3.1.3.2.4.4 Duration after Meal without Heartburn Symptoms

The number of minutes after the meal until subjects reported LOCF heartburn symptoms by treatment group is summarized below. Only subjects who reported no heartburn symptoms at the start of the meal were included in this analysis.

Summary of Duration (Minutes) After Meal without Heartburn Symptoms
Protocol RAN4006
All Subjects Population

Run-In Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	192	10.5 (1.37)	0.0	0.726	
Ranitidine 150mg	182	10.6 (1.32)	0.0	0.684	0.903
Placebo	187	10.3 (1.22)	0.0		

Copied from Table 19.
Correction was made in Adjustment to Clinical Report.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).
Only subjects who reported not having heartburn symptoms at the start of the meal were included in the analysis.

Treatment Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	177	49.5 (5.72)	7.5	0.305	
Ranitidine 150mg	181	56.9 (5.98)	22.5	0.104	0.525
Placebo	188	43.1 (5.16)	7.5		

Copied from Table 19.
Correction was made in Adjustment to Clinical Report.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).
Only subjects who reported not having heartburn symptoms at the start of the meal were included in the analysis.

As seen from tables above, during the Run-In Meal visit, the median duration without any heartburn symptoms was zero minutes in all three treatment groups. During the Treatment Meal visit, the median duration without any heartburn symptoms was numerically longest in the ranitidine 150mg group as compared to either placebo or ranitidine 75mg. The differences among the treatment groups were not statistically significant.

3.1.3.2.4.5 Largest Number of Consecutive Timepoints without Heartburn

The largest number of consecutive 15-minute post-meal evaluation timepoints (during the 40-280 minute post-meal evaluations) at which subjects had "No" LOCF heartburn symptoms, by treatment group is summarized below.

Summary of Largest Number of Consecutive Timpoints without Heartburn
Protocol RAN4006
All Subjects Population

Run-In Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	204	2.0 (0.19)	1.0	0.525	
Ranitidine 150mg	198	2.1 (0.21)	1.0	0.568	0.977
Placebo	199	2.2 (0.21)	1.0		

Copied from Table 20.
Correction was made in Adjustment to Clinical Report.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

Treatment Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	204	5.5 (0.39)	4.0	0.637	
Ranitidine 150mg	198	6.5 (0.39)	5.0	0.006	0.074
Placebo	199	4.9 (0.37)	3.0		

Copied from Table 20.
Correction was made in Adjustment to Clinical Report.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

As seen from tables above, during the Run-In visit, the median largest number of consecutive timepoints without heartburn was statistically comparable among the three treatment groups.

During the Treatment Meal visit, the median largest number of consecutive timepoints without LOCF heartburn symptoms was statistically significantly greater in the ranitidine 150mg as compared to placebo.

3.1.3.2.4.6 **Number of Timepoints without Heartburn**

The total number of 15-minute, post-meal evaluation timepoints (during the 40-280 minute post-meal evaluations) at which subjects had "No" LOCF heartburn symptoms, by treatment group is summarized below.

Summary of Number of Timepoints without Heartburn
Protocol RAN4006
All Subjects Population

Run-In Meal

Treatment	N	Mean (SD)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	204	2.4 (0.23)	1.0	0.554	
Ranitidine 150mg	198	2.5 (0.25)	1.0	0.429	0.909
Placebo	199	2.7 (0.25)	1.0		

Copied from Table 21.
Correction was made in Adjustment to Clinical Report.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

Treatment Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	204	6.4 (0.42)	4.0	0.495	
Ranitidine 150mg	198	7.6 (0.41)	7.0	0.009	0.078
Placebo	199	5.8 (0.40)	4.0		

Copied from Table 21.
Correction was made in Adjustment to Clinical Report.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

As seen from tables above, during the Run-In visit, the median number of timepoints without LOCF heartburn symptoms was not statistically different for any of the pairwise treatment group comparisons.

During the Treatment Meal visit, the median number of timepoints without LOCF heartburn symptoms was statistically significantly greater in the ranitidine 150mg group as compared to placebo.

3.1.3.2.4.7 Number of Subjects with Antacid Rescue Use

The number of subjects with antacid rescue use is summarized below.

Summary of Rescue Antacid Use
Protocol RAN4006
All Subjects Population

Run-In Meal

Treatment	Rescue Antacid Use	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	53/204 (26%)	0.630	
Ranitidine 150mg	56/198 (28%)	0.859	0.599
Placebo	56/199 (28%)		

Copied from Table 22.
P-values were calculated using Mantel-Haenszel test stratified by investigator.

Treatment Meal

Treatment	Rescue Antacid Use	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	19/204 (9%)	0.269	
Ranitidine 150mg	12/198 (6%)	0.018	0.189
Placebo	26/199 (13%)		

Copied from Table 22.
P-values were calculated using Mantel-Haenszel test stratified by investigator.

As seen from tables above, during the Run-In Meal, there were no significantly differences between the treatment groups in the percentage of subjects who used rescue antacid.

During the Treatment Meal visit, a statistically significantly lower percentage of subjects used rescue antacid in the ranitidine 150mg group as compared to placebo.

3.1.3.2.4.8 Subject Global Evaluation

The results of the subject's global evaluation at the Run-In and Treatment Meal visits, by treatment group are summarized below.

Summary of Subject Global Evaluation
Protocol RAN4006
All Subjects Population

	Ranitidine 75mg N=204	Ranitidine 150mg N=198	Placebo N=199
Run-In Meal			
N	204	198	199
Subject Global Score			
0=No Effect	41 (20%)	45 (23%)	39 (20%)
1=Poor	38 (19%)	36 (18%)	38 (19%)
2=Fair	48 (24%)	46 (23%)	46 (23%)
3=Good	39 (19%)	36 (18%)	34 (17%)
4=Very Good	22 (11%)	21 (11%)	31 (16%)
5=Excellent	16 (8%)	14 (7%)	11 (6%)
Mean of subject global score	2.1	2.0	2.1
Median of subject global score	2.0	2.0	2.0
Comparison with Placebo	0.912	0.590	
Comparison with Ranitidine 75mg		0.441	
Treatment Meal			
N	204	198	199
Subject Global Score			
0=No Effect	8 (4%)	7 (4%)	8 (4%)
1=Poor	16 (8%)	7 (4%)	15 (8%)
2=Fair	36 (18%)	33 (17%)	35 (18%)
3=Good	52 (25%)	53 (27%)	55 (28%)
4=Very Good	61 (30%)	58 (29%)	63 (32%)
5=Excellent	31 (15%)	40 (20%)	22 (11%)
Mean of subject global score	3.2	3.4	3.1
Median of subject global score	3.0	3.0	3.0
Comparison with Placebo	0.698	0.060	
Comparison with Ranitidine 75mg		0.193	

Copied from Table 24.
Correction was made in Adjustment to Clinical Report.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

As seen from table above, during the Run-In Meal visit, subjects' median global evaluation scores were the same for all three treatment groups and there were no statistically significant differences.

During the Treatment Meal visit, the median global evaluation score was 3.0 for each of the treatment groups. Comparison of the rank differences in global assessment between treatment groups revealed that the ranitidine 150mg group was numerically better than the placebo group.

3.1.3.3 Reviewer's Comments and Evaluation

3.1.3.3.1 Disproportional Protocol Deviation

There was disproportionate proportion of subjects who deviated from study protocol among treatment group (p=0.0159). The ranitidine 75mg group had higher proportion of subjects who deviated from study protocol than the placebo group (25% vs.16%; p=0.0040).

3.1.3.3.2 Multiplicity Issue

In the protocol it stated the application of this Bonferroni-Holm adjustment was performed in a hierarchical fashion. Each of the active treatments was first compared to placebo at an $\alpha/2$ (0.025) level of significance. If either of these two active treatments was statistically significantly superior to placebo, the two active treatments were compared at a 0.05 level of significance.

The only comparisons of interest for this review are ranitidine 150mg versus placebo and ranitidine 150mg versus ranitidine 75mg. The p-values for ranitidine 150mg vs. placebo comparisons are shown to confirm that the testing procedure was followed.

3.1.3.3.3 LOCF Analyses

The comments stated for Protocol RAN3016 also apply to this study.

3.1.3.3.4 Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Endpoint

3.1.3.3.4.1 Imbalance in Heartburn Severity AUC at the Run-In Meal Visit

It was found that at the Run-In Meal visit, there was a statistically significant difference in mean heartburn severity AUC in subjects later randomized to ranitidine 150mg compared to subjects later randomized to ranitidine 75mg(p=0.050) for the Intent-to-Treat population. Similarly, the mean AUC for the ranitidine 150mg group was numerically higher than for subjects later randomized to placebo (174.0 vs. 159.8).

The sponsor performed the analyses of mean heartburn severity AUC after adjusting for several demographic and heartburn history characteristics as well as Run-In Meal AUC. This analysis should be considered as a post-hoc analysis and hypothesis generating. The results from these analyses are given below.

Summary of Heartburn Severity Area under the Curve (AUC) in mm·Hr
Adjusted for Investigator, Run-In Meal AUC, and
Demographic and Heartburn History Characteristics
Protocol RAN4006
All Subjects Population

Run-In Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	201	157.2 (5.72)	147.0	0.734	
Ranitidine 150mg	198	174.0 (6.28)	168.5	0.085	0.039
Placebo	199	159.8 (6.08)	149.7		

Copied from Table 10.01.
P-values were calculated using ANOVA, adjusting for investigator.

Treatment Meal

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	201	75.9 (5.74)	42.2	0.277	
Ranitidine 150mg	198	63.8 (5.24)	36.6	<0.001	0.009
Placebo	199	85.0 (5.81)	62.3		

Copied from Table 10.01.
P-values were calculated using ANOVA, adjusting for investigator, Run-In Meal AUC, demographic and heartburn history characteristics. .

As seen from table above, in this analysis, it was shown that at the Treatment Meal visit, that adjusting for investigator, Run-In Meal AUC, and some demographic and heartburn history characteristics, there were a statistically significant difference in mean heartburn severity AUC between the ranitidine 150mg and placebo treatment groups for the all subject population. Contrary to the results from the pre-specified primary analysis, ranitidine 150mg was statistical significant different from ranitidine 75mg.

3.1.3.3.4.2 Heartburn Severity AUC

For the pre-specified primary endpoint, heartburn severity AUC, it was shown that at the Treatment Meal visit, that there was a statistically significant difference in mean heartburn severity AUC between the ranitidine 150mg and placebo treatment groups for all subjects population. But, for efficacy evaluable population, at the Treatment Meal visit, mean heartburn severity AUC of the ranitidine 150mg group was numerically lower than that of placebo. It failed to achieve statistical significance level of 0.025. The treatment differences of means between ranitidine 150mg and placebo were 21.2 mm·hr and 16.3 mm·hr for Intent-to-Treat and efficacy evaluation populations, respectively.

There was no statistically significant difference between the ranitidine 150mg and ranitidine 75 groups. However, there was a trend in favor of ranitidine 150mg over ranitidine 75mg in the all subjects population (p=0.102) not in the efficacy evaluable population (p=0.563). The treatment differences of means between ranitidine 150mg and

ranitidine 75mg were 12.1 mm·hr and 5.5 mm·hr for Intent-to-Treat and efficacy evaluation populations, respectively.

3.1.3.3.4.3 **Three Clinical Endpoints**

These analyses of three clinical endpoints were considered as post-hoc analyses. However, this study showed statistically significant differences between ranitidine 150mg and placebo for all three clinical endpoints. There was a trend for all three clinical endpoints in favor of ranitidine 150mg over ranitidine 75mg. The treatment differences were about 9% for all three clinical endpoint.

3.1.3.3.4.4 **Subgroup Analysis**

The sponsor also performed subgroup analyses of the primary efficacy endpoint by race (white vs. non-white), gender, and age (<65 vs. ≥65). The results for subgroup analyses are given below.

Treatment Meal Heartburn Severity AUC for by Subgroup
Protocol RAN4006
Intent-to-Treat Population

	Ranitidine 75mg			Ranitidine 150mg			Placebo			Ran 75mg vs Placebo	Ran 150mg vs. Placebo	Ran 75mg vs. Ran 150mg
Subgroup	N	Mean	Median	N	Mean	Median	N	Mean	Median	P-value	P-value	P-value
Race												
White	159	70.3	38.8	155	61.7	34.3	155	76.9	55.6	0.614	0.068	0.182
Non-white	42	97.1	55.9	43	71.6	48.8	44	113.6	75.3	0.109	0.031	0.581
Gender												
Male	87	62.7	31.6	80	58.7	33.9	81	75.7	45.5	0.235	0.103	0.632
Female	114	85.9	54.3	118	67.3	37.8	118	91.4	66.6	0.553	0.033	0.133
Age												
<65	189	75.3	41.3	180	65.3	37.0	183	81.8	56.9	0.476	0.035	0.155
≥65	12	84.5	71.9	18	49.5	13.3	16	122.5	114.5	0.096	0.220	0.619

Copied from Tables 10.26-10.31.
P-values were calculated using a ANOVA, adjusting for by investigator.

As seen from table above, superiority of ranitidine 150mg over placebo was consistent across gender and race. The number of elderly subjects was too small for a meaningful statistical comparison by age.

3.1.3.3.5 **Reviewer's Comments on Sponsor's Analysis of Secondary Endpoint**

This study indicated that the ranitidine 150mg was more effective than placebo in 5 of 8 secondary efficacy endpoints: reduction in AUC, peak heartburn, largest number of consecutive timepoints without heartburn, number of timepoint without heartburn, and

antacid rescue use. It failed to achieve statistical significance level of 0.025 for subject global evaluation.

3.1.3.3.5.1 **Reduction of Heartburn Severity**

At the Run-In Meal visit, there was a statistically significant difference in mean heartburn severity AUC in subjects later randomized to ranitidine 150mg compared to subjects later randomized to ranitidine 75mg(p=0.050) for the Intent-to-Treat population. Similarly, the mean AUC for the ranitidine 150mg group was numerically higher than for subjects later randomized to placebo (174.0 vs. 159.8).

The results from the sponsor's analyses of reduction and the percentage reduction in heartburn severity AUC from the Run-In Meal visit to Treatment Meal visit tended to be bias in favor of ranitidine 150mg due to imbalance at the Run-In Meal visit. The analyses of reduction and the percentage reduction in heartburn severity AUC from the Run-In Meal visit to Treatment Meal visit should be adjusted for the Run-In Meal peak heartburn severity LOCF.

3.1.3.3.5.2 **Peak Heartburn Severity LOCF Score**

It was found that at the Run-In Meal visit, the median peak heartburn severity LOCF score of the ranitidine 150mg group was, however, numerically greater than the placebo (68.5 vs. 63.0; p=0.061).

The results from the sponsor's analyses of peak heartburn severity LOCF score at the Treatment Meal visit and reduction in peak heartburn severity from the Run-In Meal visit to Treatment Meal visit tended to be bias in favor of ranitidine 150mg due to imbalance at the Run-In Meal visit. The analysis of peak heartburn severity LOCF score at the Treatment Meal visit should be adjusted for the Run-In Meal peak heartburn severity LOCF.

3.2 Evaluation of Safety

In Study RAN3016, the overall incidence of adverse events during the Treatment phase of the study was low. There were no statistically significant differences between the treatment groups: 16 (5%) subjects in the ranitidine 150mg group; 6 (2%) subjects in the ranitidine 75mg group; and 16 (5%) subjects in the placebo group reported at least one adverse event.

In Study RAN3018, during the Treatment Phase, the proportion of subjects' experiencing any adverse event was not statistically different across treatment groups: 3 (<1%) subjects in the ranitidine 150mg group, 4 (1%) subjects in the ranitidine 75mg group, and 4 (1%) subjects in the placebo group reported at least one adverse event.

In Study RAN4006, during the Treatment Phase, the proportion of subjects' experiencing any adverse event was not statistically different across treatment groups: 2 (1%) subjects

in the ranitidine 150mg group, 4 (2%) subjects in the ranitidine 75mg group, and 4 (2%) subjects in the placebo group reported at least one adverse event.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The results of subgroup analyses of the primary efficacy endpoint by race (White vs. non-White), gender, and age (<65 vs. ≥65) for studies RAN3016, RAN3018, and RAN4006 are given below.

Treatment Meal Heartburn Severity AUC for by Subgroup
Protocol RAN3016
Intent-to-Treat Population

Subgroup	Ranitidine 75mg N	Mean	Median	Ranitidine 150mg N	Mean	Median	Placebo N	Mean	Median	Ran 75mg vs Placebo P-value	Ran 150mg vs. Placebo P-value	Ran 75mg vs. Ran 150mg P-value
Race												
White	210	90.3	67.8	225	92.9	66.6	220	114.9	87.5	0.007	0.002	0.704
Non-White	109	120.6	104.3	95	121.2	103.6	102	135.4	129.3	0.814	0.319	0.439
Gender												
Male	115	90.8	69.3	111	91.9	66.6	127	107.2	76.8	0.100	0.108	0.980
Female	204	106.2	86.8	209	106.3	74.8	195	130.6	118.1	0.024	0.004	0.522
Age												
<65	306	98.6	80.1	304	103.7	73.7	304	120.3	97.4	0.010	0.007	0.927
≥65	13	148.7	115.6	16	54.8	10.9	18	139.5	133.8	0.224	0.005	0.156

Copied from Tables 10.37-10.42.
P-values were calculated using a ANOVA, adjusting for by investigator and Run-In Meal AUC.

Treatment Meal Heartburn Severity AUC for by Subgroup
Protocol RAN3018
Intent-to-Treat Population

Subgroup	Ranitidine 75mg N	Mean	Median	Ranitidine 150mg N	Mean	Median	Placebo N	Mean	Median	Ran 75mg vs Placebo P-value	Ran 150mg vs. Placebo P-value	Ran 75mg vs. Ran 150mg P-value
Race												
White	241	77.0	51.1	235	85.4	45.5	224	90.4	66.1	0.024	0.330	0.194
Non-white	68	129.5	91.1	71	124.9	120.4	82	121.8	115.7	0.127	0.947	0.152
Gender												
Male	110	75.2	47.8	114	66.4	32.5	99	98.5	82.2	0.012	0.011	0.960
Female	199	96.0	80.8	192	111.3	74.3	207	99.0	79.3	0.560	0.506	0.219
Age												
<65	292	88.1	62.8	285	92.6	54.0	293	98.7	79.3	0.085	0.293	0.509
≥65	17	97.1	93.8	21	121.1	110.5	13	102.2	83.2	0.169	0.346	0.725

Copied from Tables 10.39-10.44.
P-values were calculated using a ANOVA, adjusting for by investigator and Run-In Meal AUC.

Treatment Meal Heartburn Severity AUC for by Subgroup
Protocol RAN4006
Intent-to-Treat Population

Subgroup	Ranitidine 75mg N	Mean	Median	Ranitidine 150mg N	Mean	Median	Placebo N	Mean	Median	Ran 75mg vs Placebo P-value	Ran 150mg vs. Placebo P-value	Ran 75mg vs. Ran 150mg P-value
Race												
White	159	70.3	38.8	155	61.7	34.3	155	76.9	55.6	0.614	0.068	0.182
Non-white	42	97.1	55.9	43	71.6	48.8	44	113.6	75.3	0.109	0.031	0.581
Gender												
Male	87	62.7	31.6	80	58.7	33.9	81	75.7	45.5	0.235	0.103	0.632
Female	114	85.9	54.3	118	67.3	37.8	118	91.4	66.6	0.553	0.033	0.133
Age												
<65	189	75.3	41.3	180	65.3	37.0	183	81.8	56.9	0.476	0.035	0.155
≥65	12	84.5	71.9	18	49.5	13.3	16	122.5	114.5	0.096	0.220	0.619

Copied from Tables 10.26-10.31.
P-values were calculated using a ANOVA, adjusting for by investigator.

As seen from tables above, non-White subjects tended to have higher mean heartburn severity AUC than White subjects. Further discussion of results in these groups can be found under the evaluation of each individual study.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

In both studies (RAN3016 and RAN4006), it stated in the protocol that the application of this Bonferroni-Holm adjustment was performed in a hierarchical fashion. Each of the active treatments was first compared to placebo at an $\alpha/2$ (0.025) level of significance. If either of these two active treatments was statistically significantly superior to placebo, the two active treatments were compared at a 0.05 level of significance.

For study RAN3016, per the protocol amendment, three pairwise comparisons could be performed for each parameter: ranitidine 150mg vs. placebo; ranitidine 75mg vs. placebo; and ranitidine 150mg vs. ranitidine 75mg. First, ranitidine 150mg was compared to placebo at the α=0.05 level of significance. Second, only if the first comparison was statistically significant, then ranitidine 75mg was compared to placebo at the α=0.05 level of significance. Third, if both of these two comparisons were statistically significant, the final comparison between ranitidine 150mg and ranitidine 75mg was performed at the α=0.05 level of significance.

'Furthermore, for study RAN3018, it was pre-specified in the protocol to use a stepdown hierarchical method for multiplicity. Pairwise comparisons between treatment groups were done in a stepdown hierarchical manner. Since the ranitidine 150mg vs. placebo was the comparison of most interest, and was expected to be the largest, this difference was tested at the alpha=0.05 level. If this value was less than or equal to 0.05, the other two pairwise comparisons (ranitidine 75mg vs. placebo and ranitidine 150mg vs. ranitidine 75mg) was made, each at the alpha=0.05 level.

In study RAN3018, it was also pre-specified to define "ranitidine 150mg was considered superior to ranitidine 75mg." For all endpoint assessments, ranitidine 150mg was considered superior to ranitidine 75mg when ranitidine 150mg was statistical significantly superior to placebo and ranitidine 75mg was not, or in the event both treatments were statistically significantly superior to placebo, when ranitidine 150mg was statistically significantly superior to ranitidine 75mg.

The only comparisons of interest for this review are ranitidine 150mg versus placebo and ranitidine 150mg versus ranitidine 75mg. The p-values for ranitidine 150mg vs. placebo and ranitidine 150mg vs. ranitidine 75mg comparisons are shown to confirm that the testing procedure was followed.

For the pre-specified primary endpoint, heartburn severity AUC, study RAN3016 showed that at the Treatment Meal visit, that there was a statistically significant difference in mean heartburn severity AUC between the ranitidine 150mg and placebo treatment groups for both Intent-to-Treat and efficacy evaluable populations. The treatment differences of means between ranitidine 150mg and placebo were 20.1 mm·hr and 16.9 mm·hr for Intent-to-Treat and efficacy evaluation populations, respectively.

There was no statistically significant difference between the ranitidine 150mg and ranitidine 75 groups. The treatment differences of means between ranitidine 150mg and ranitidine 75mg were 0.6 mm·hr and 1.4 mm·hr for Intent-to-Treat and efficacy evaluation populations, respectively, in favor of ranitidine 75mg group.

For the post-hoc analyses of FDA defined three clinical endpoints, this study showed statistically significant differences between ranitidine 150mg and placebo for all three clinical endpoints. The treatment differences of between ranitidine 150mg and ranitidine 75mg ranged from 4% to 7% for all three endpoints in favor of ranitidine 150mg. This study also revealed that the ranitidine 150mg was more effective than placebo in 3 of 8 secondary efficacy endpoints: reduction of heartburn severity, peak heartburn severity, and subject global evaluation.

For more clinical meaningful endpoint, prevention of heartburn, pre-specified in the protocol as a secondary efficacy endpoint, treatment groups did not differ significantly in the number of subjects achieving complete prevention during the Treatment Meal visit.

Study RAN3018 indicated that at the Treatment Meal visit, that there was not statistically significant difference in mean heartburn severity AUC between the ranitidine 150mg and

placebo treatment groups for both Intent-to-Treat and efficacy evaluable populations. The treatment differences of means between ranitidine 150mg and placebo were 4.2 mm·hr and 6.9 mm·hr for Intent-to-Treat and efficacy evaluation populations, respectively.

There was no statistically significant difference between the ranitidine 150mg and ranitidine 75mg groups. The treatment differences of means between ranitidine 150mg and ranitidine 75mg were 6.0 mm·hr and 1.1 mm·hr for Intent-to-Treat and efficacy evaluation populations, respectively, in favor of ranitidine 75mg group.

This study revealed that the ranitidine 150mg was more effective than placebo in only 1 of 7 secondary efficacy endpoints: subject global evaluation. It failed to achieve statistical significance level of 0.025 in these two secondary efficacy endpoints: largest number of consecutive timepoints without heartburn and number of timepoint without heartburn.

For more clinical meaningful endpoint, prevention of heartburn, pre-specified in the protocol as a secondary efficacy endpoint, treatment groups did not differ significantly in the number of subjects achieving complete prevention during the Treatment Meal visit.

Study RAN4006 showed that at the Treatment Meal visit, that there was a statistically significant difference in mean heartburn severity AUC between the ranitidine 150mg and placebo treatment groups for all subjects population. But, for efficacy evaluable population, at the Treatment Meal visit, mean heartburn severity AUC of the ranitidine 150mg group was numerically lower than that of placebo. It failed to achieve statistical significance level of 0.025. The treatment differences of means between ranitidine 150mg and placebo were 21.2 mm·hr and 16.3 mm·hr for Intent-to-Treat and efficacy evaluation populations, respectively.

There was no statistically significant difference between the ranitidine 150mg and ranitidine 75 groups. However, there was a trend in favor of ranitidine 150mg over ranitidine 75mg in the all subjects population ($p=0.102$) not in the efficacy evaluable population ($p=0.563$). The treatment differences of means between ranitidine 150mg and ranitidine 75mg were 12.1 mm·hr and 5.5 mm·hr for Intent-to-Treat and efficacy evaluation populations, respectively.

For the post-hoc analyses of FDA defined three clinical endpoints, this study showed statistically significant differences between ranitidine 150mg and placebo for all three clinical endpoints. There was a trend for all three clinical endpoints in favor of ranitidine 150mg over ranitidine 75mg. The treatment differences were about 9% for all three clinical endpoint.

This study indicated that the ranitidine 150mg was more effective than placebo in 5 of 8 secondary efficacy endpoints: reduction in AUC, peak heartburn, largest number of consecutive timepoints without heartburn, number of timepoint without heartburn, and antacid rescue use. It failed to achieve statistical significance level of 0.025 for subject global evaluation.

For more clinical meaningful endpoint, prevention of heartburn, pre-specified in the protocol as a secondary efficacy endpoint, treatment groups did not differ significantly in the number of subjects achieving complete prevention during the Treatment Meal visit.

5.2 Conclusion and Recommendations

The sponsor has submitted three placebo-controlled studies (RAN3016, RAN3018, and RAN4006) in support of the proposed claim.

In Study RAN3016, ranitidine 150mg was more effective than placebo in terms of pre-specified primary efficacy endpoint, three clinical endpoints defined by FDA, and 3 of 8 secondary efficacy endpoints (reduction of heartburn severity, peak heartburn severity, and subject global evaluation). For more clinical meaningful clinical endpoint, complete prevention, which was pre-specified as a secondary efficacy endpoint, ranitidine 150mg was not statistically different from placebo.

In Study RAN3018, ranitidine 150mg was not statistically significant different from placebo in terms of pre-specified primary efficacy endpoint, one of three clinical endpoints defined by FDA, and 6 of 7 secondary efficacy endpoints. There was a slightly trend in favor of ranitidine 150mg over placebo. For more clinical meaningful clinical endpoint, complete prevention, which was pre-specified as a secondary efficacy endpoint, ranitidine 150mg was not statistically different from placebo.

In Study RAN4006, ranitidine 150mg was statistically significant different from placebo in terms of pre-specified primary efficacy endpoint, three clinical endpoints defined by FDA, and 5 of 8 secondary efficacy endpoints (reduction of heartburn severity, peak heartburn severity, largest number of consecutive timepoints without heartburn, number of timepoints without heartburn, and number of subjects with antacid rescue use). For more clinical meaningful clinical endpoint, complete prevention, ranitidine 150mg was not statistically different from placebo.

In conclusion, two of the three clinical studies (RANA3016 and RANA4006) suggest that ranitidine 150mg was more effective than placebo for reducing severity of meal-induced heartburn when taken right before meal. In the other study (RAN3018), the ranitidine 150mg was not significantly better than placebo for the primary and most secondary efficacy parameters.

6. APPENDIX

Table 1 Baseline Patient Characteristic by Treatment Group --- Protocol RANA3016
Intent-To-Treat Population

Characteristic	Ranitidine 75 mg (N=320)	Ranitidine 150 mg (N=320)	Placebo (N=322)	Among Groups p-value
Gender				0.4322
Male	115 (36%)	111 (35%)	127 (39%)	
Female	205 (64%)	209 (65%)	195 (61%)	
Race				0.4331
Caucasian	210 (66%)	225 (70%)	220 (68%)	
Black	86 (27%)	68 (21%)	80 (25%)	
Hispanic	23 (7%)	25 (8%)	19 (6%)	
Oriental	0	0	2 (1%)	
Other	1 (<1%)	2 (<1%)	1 (<1%)	
Age (yr)				0.4586
Mean (SD)	40.8 (13.0)	41.9 (12.2)	41.8 (12.4)	
Height (inches)				0.4835
Mean (SD)	66.3 (3.8)	66.5 (3.9)	66.7 (4.0)	
Weight (lbs)				0.7422
Mean (SD)	187.9 (44.9)	191.9 (48.8)	188.2 (44.8)	
Tobacco Use				0.8214
Daily User	88 (28%)	81 (25%)	85 (26%)	
Non-Daily User	232 (73%)	239 (75%)	237 (74%)	
Number of days in a typical month with heartburn, acid indigestion or sour stomach				
Mean (SD)	25.2 (4.1)	25.6 (3.9)	25.4 (4.1)	
Do you get heartburn at night?				0.7062
No	20 (6%)	23 (7%)	18 (6%)	
Yes	300 (94%)	297 (93%)	304 (94%)	
Did you ever see a doctor because of your heartburn, sour stomach or acid indigestion				0.6732
No	210 (66%)	211 (66%)	221 (69%)	
Yes	110 (34%)	109 (34%)	101 (31%)	

Copied from Tables 4 and 9.
P-value was calculated using Kruskal-Wallis test for continuous data.
P-value was calculated using Cochran-Mantel-Haenszel test for categorical data.
P-values were obtained by this reviewer.

Table 1 Baseline Patient Characteristic by Treatment Group (Continued) --- Protocol RANA3016

Intent-To-Treat Population

Characteristic	Ranitidine 75 mg (N=320)	Ranitidine 150 mg (N=320)	Placebo (N=322)	Among Groups p-value
How many days per week over the last two months, have you experience meal related episodes of heartburn?				0.1649
5 days per week	125 (39%)	103 (32%)	116 (36%)	
6 days per week	76 (24%)	74 (23%)	64 (20%)	
7 days per week	119 (37%)	143 (45%)	141 (44%)	

Copied from Tables 4 and 9.
P-value was calculated using Kruskal-Wallis test for continuous data.
P-value was calculated using Cochran-Mantel-Haenszel test for categorical data.
P-values were obtained by this reviewer.

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Table 2 Baseline Patient Characteristic by Treatment Group --- Protocol RANA3018
Intent-To-Treat Population

Characteristic	Ranitidine 75 mg (N=309)	Ranitidine 150 mg (N=306)	Placebo (N=306)	Among Groups p-value
Gender				0.4339
Male	110 (36%)	114 (37%)	99 (32%)	
Female	199 (64%)	192 (63%)	207 (68%)	
Race				0.3881
Caucasian	241 (78%)	235 (77%)	224 (73%)	
Black	58 (19%)	54 (18%)	63 (21%)	
Hispanic	6 (2%)	11 (4%)	13 (4%)	
Oriental	0	2	0	
Other	4 (1%)	4 (1%)	6 (2%)	
Age (yr)				0.1440
Mean (SD)	41.7 (13.2)	43.2 (12.8)	41.5 (12.5)	
Height (inches)				0.5974
N	309	305	306	
Mean (SD)	66.2 (3.8)	66.5 (4.0)	66.2 (4.0)	
Weight (lbs)				0.9611
N	309	305	305	
Mean (SD)	189.5 (49.1)	189.4 (46.8)	190.4 (48.0)	
Tobacco Use				0.5967
Daily User	81 (26%)	87 (28%)	76 (25%)	
Non-Daily User	228 (74%)	219 (72%)	230 (75%)	
Number of days in a typical month with heartburn, acid indigestion or sour stomach				
Mean (SD)	25.0 (4.2)	25.0 (4.0)	25.1 (4.2)	
Do you get heartburn at night?				0.4210
No	12 (4%)	19 (6%)	16 (5%)	
Yes	297 (96%)	287 (94%)	290 (95%)	
Did you ever see a doctor because of your heartburn, sour stomach or acid indigestion				0.3556
No	208 (67%)	206 (67%)	195 (64%)	
Yes	101 (33%)	100 (33%)	111 (36%)	
How many days per week over the last two months, have you experience meal related episodes of heartburn?				0.9192
5 days per week	123 (40%)	127 (42%)	126 (41%)	
6 days per week	78 (25%)	76 (25%)	71 (23%)	
7 days per week	108 (35%)	103 (34%)	109 (36%)	

Copied from Tables 4 and 9. P-values were calculated using Kruskal-Wallis test for continuous data and using Cochran-Mantel-Haenszel test for categorical data .P-values were obtained by this reviewer.

Table 3 Baseline Patient Characteristic by Treatment Group --- Protocol RANA4006 Intent-To-Treat Population

Characteristic	Ranitidine 75 mg (N=204)	Ranitidine 150 mg (N=198)	Placebo (N=199)	Among Groups p-value
Gender				0.8296
Male	88 (43%)	80 (40%)	81 (41%)	
Female	116 (57%)	118 (60%)	118 (59%)	
Race				0.9344
Caucasian	161 (79%)	155 (78%)	155 (78%)	
Black	21 (10%)	20 (10%)	23 (12%)	
Hispanic	19 (9%)	19 (10%)	16 (8%)	
Oriental	1 (<1%)	1 (<1%)	0	
Other	2 (<1%)	3 (2%)	5 (3%)	
Age (yr)				0.1766
Mean (SD)	45.4 (13.3)	43.3 (14.3)	43.7 (13.3)	
Height (inches)				0.6672
Mean (SD)	66.3 (4.0)	66.6 (3.8)	66.6 (3.9)	
Weight (lbs)				0.7393
Mean (SD)	187.9 (47.6)	190.9 (46.3)	188.9 (44.8)	
Tobacco Use				0.0544
Daily User	49 (24%)	47 (24%)	66 (33%)	
Non-Daily User	155 (76%)	151 (76%)	133 (67%)	
Number of days in a typical month with heartburn, acid indigestion or sour stomach				
Mean (SD)	26.6 (4.1)	27.1 (3.8)	26.3 (3.8)	
Do you get heartburn at night?				0.9428
No	14 (7%)	13 (7%)	12 (6%)	
Yes	190 (93%)	185 (93%)	187 (94%)	
Did you ever see a doctor because of your heartburn, sour stomach or acid indigestion				0.4604
No	119 (58%)	104 (53%)	114 (57%)	
Yes	85 (42%)	94 (47%)	85 (43%)	
How many days per week over the last two months, have you experience meal related episodes of heartburn?				0.1588
5 days per week	40 (20%)	31 (16%)	37 (19%)	
6 days per week	25 (12%)	19 (10%)	26 (13%)	
7 days per week	42 (21%)	26 (13%)	33 (17%)	
More than 7 times per week	97 (48%)	122 (62%)	103 (52%)	

Copied from Tables 4 and 9. P-values were calculated using Kruskal-Wallis test for continuous data and using Cochran-Mantel-Haenszel test for categorical data .P-values were obtained by this reviewer.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-698
Drug Name:	OTC Zantac 150 (ranitidine 150mg) tablet
Indication(s):	Treatment of heartburn (Separate review for prevention of heartburn)
Applicant:	Pfizer Consumer Healthcare
Date(s):	NDA dated October 31, 2003
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II (HFD-715)
Statistical Reviewer:	Milton C. Fan, Ph.D. (HFD-715)
Concurring Reviewers:	Stella Grosser, Ph.D. (HFD-715)
Medical Division:	Gastrointestinal and Coagulant Drug Product (HFD-180)
Clinical Team:	Eric Brodsky, M.D. (HFD-180)
Project Manager:	Diane Moore (HFD-180)

Keywords: clinical study, LOCF, AUC, multiplicity, placebo-controlled

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The sponsor has submitted two controlled efficacy study (RAN3013 and RAN3014) in support of the proposed claim for ranitidine 150mg for treatment of heartburn.

In Study RAN3013, for the pre-specified primary endpoint, total pain relief score (TOTPAR) of severe or very severe heartburn over 2-hour evaluation period for first episode, it was shown that there was a statistically significant difference in TOTPAR score between the ranitidine 150mg and placebo for both Intent-to-Treat and efficacy evaluable populations. There was a statistically significant difference in TOTPAR score between the ranitidine 75mg and placebo for the Intent-to-Treat population. For efficacy evaluable population, the treatment difference between ranitidine 75mg and placebo just failed to reach statistical significance level of 0.0167 adjusting for multiple comparisons. There was no statistically significant difference between the ranitidine 150mg and ranitidine 75 groups.

For total pain relief score (TOTPAR) of severe or very severe heartburn over 2-hour evaluation period for all study drug-treated episodes, it was shown that there were statistically significant differences in TOTPAR scores between the ranitidine 150mg and placebo and between ranitidine 75mg and placebo for both Intent-to-Treat and efficacy evaluable populations. There was no statistically significant difference between ranitidine 75mg and ranitidine 150mg.

This study revealed that both ranitidine 75mg and ranitidine 150mg groups were more effective than placebo in 3 of 8 secondary efficacy endpoints: subject's overall assessment of study drug efficacy for each episode of severe heartburn, subject's global evaluation, and peak relief of severe heartburn episodes.

In Study RAN3014, for the pre-specified primary endpoint, total pain relief score (TOTPAR) of severe or very severe heartburn over 2-hour evaluation period for first episode, it was shown that after adjusting for multiple comparisons, there was not statistically significant difference in TOTPAR score between the ranitidine 150mg and placebo groups for both Intent-to-Treat and efficacy evaluable populations. There was not statistically significant difference in TOTPAR score between the ranitidine 75mg and placebo groups for both Intent-to-Treat and efficacy evaluable populations. There was no statistically significant difference between the ranitidine 150mg and ranitidine 75 groups.

For total pain relief score (TOTPAR) of severe or very severe heartburn over 2-hour evaluation period for all study drug-treated episodes, it was shown that there were statistically significant differences in TOTPAR scores between the ranitidine 150mg and placebo for the Intent-to-Treat population. For efficacy evaluable population, it failed to achieve statistical significance level of 0.0167 adjusting for multiple comparisons.. The ranitidine 75mg was not statistically significantly different from placebo. No statistically significant difference was observed between ranitidine groups.

This study revealed that the ranitidine 150mg group was more effective than placebo in 3 of 8 secondary efficacy endpoints: subject's overall assessment of study drug efficacy for each episode of severe heartburn, subject's global evaluation, and rescue antacid use.

The ranitidine 75mg group was more effective than placebo in 4 of 8 secondary efficacy endpoints: subject's overall assessment of study drug efficacy for each episode of severe heartburn, subject's global evaluation, rescue antacid use and change in AGIDA scores for subjects who treated severe heartburn episodes.

In conclusion, only Study RANA3013 demonstrated that both ranitidine 75mg and ranitidine 150mg were statistically significantly better than placebo for first study drug treated episode for analysis of total pain relief (TOTPAR). Study 3014 showed dose related trends, though the difference between ranitidine 150mg and ranitidine 75mg was not statistically significant.

1.2 Brief Overview of Clinical Studies

1.2.1 Study RAN3013

This study was a randomized, multicenter (23 sites), double-blind, placebo-controlled, parallel group, ambulatory outpatient study with a single-blind placebo Run-In Phase comparing ranitidine 150mg, ranitidine 75mg and placebo in the treatment of severe heartburn episodes. This study was conducted in the US.

The primary objective of this study was to compare the efficacy of ranitidine 150mg to ranitidine 75mg and placebo when taken as needed up to twice daily for two weeks in adults for severe heartburn episodes.

Eligible subjects had the following criteria to participate in this study:

- at least 1 year history of heartburn, sour stomach, or acid indigestion, typically brought on by eating, stress, or postural changes.
- report almost daily heartburn during the two weeks prior to Visit 1 (i.e., at least five of seven days each week in the two weeks prior to Visit 1)
- describe most of their heartburn episodes as being severe or very severe in the two weeks prior to Visit 1 (using the following five-point scale: very mild, mild, moderate, severe, or very severe).

All eligible screened subjects were scheduled for Visit 1. Subjects who qualified entered into the one week Run-In Phase and used single blind study drug (placebo) to treat up to two heartburn episodes (regardless of severity) per day for a period of one week. Maalox was provided to treat heartburn episodes which were not relieved by study drug or were in excess of the two treated by study drug per day.

At Visit 2, those subjects who met the following criteria qualified for participation in the Treatment Phase of the study and were randomized to the double-blind phase of the study for a total of 14 days:

- treated heartburn episodes on at least four of the first seven days during the one week Run-In Phase
- had at least 50% of these episodes rated as severe or very severe (5 point scale: very mild, mild, moderate, severe, and very severe)

Subjects who qualified for entry after the Run-In Phase were randomized to receive either placebo, 75 mg ranitidine, or 150 mg ranitidine, for up to twice daily use, for a total of 14 days, for the treatment of severe or very serve heartburn episodes.

Subjects took the study drug as needed to treat up to two severe or very severe episodes per day. They were also given rescue antacid of Maalox.

Subject was instructed to take the study drug as follows:

- Subject might treat up to two severe or very severe heartburn episodes per day.
- Subject might only take one dose of study drug to treat each heartburn episode considered by the subject to be severe or very severe.
- Subject might not take more than two doses of study drug in any calendar day.
- For severe or very severe heartburn episodes that were not relieved by the study drug, subject should take the supplied rescue antacid, beginning two hours after ingesting study drug, until that heartburn episode was relieved.
- If the heartburn episode was not considered by the subject to be severe or very severe, the subject should take the supplied rescue antacid tablets, i.e., chewed 1-2 tablets and repeated as needed until that episode of heartburn was relieved.
- If antacid tablets were used to treat a non-severe heartburn episode, under no circumstances might study drug be used to later treat that same episode.
- Subject might not treat a new episode of severe or very severe heartburn with another dose of study drug until the previous heartburn episode had been relieved and at least two hours had elapsed since the previous dose of study drug was taken.
- If a subject had a second severe or very severe heartburn episode at least 2 hours following the ingestion of the first dose of study drug for that day, the subject might ingest the second and final dose of study drug for the calendar day for the treatment of this episode.
- If a subject had treated two severe or very severe heartburn episodes in a calendar day with study drug, all other heartburn episodes regardless of severity might only be treated with only the supplied rescue antacids.

Subjects completed a Diary to assess the severity of all heartburn episodes for each day of the Treatment Phase and heartburn relief for two hours following treatment with study drug for severe or very severe heartburn episodes. Subject completed an overall assessment of study drug efficacy using 6 point scales (not effective, poor, fair, good, very good, and excellent) for each episode of severe or very severe heartburn treated with

study drug. Each morning subjects assessed if nighttime heartburn interfered with their sleep with yes/no.

All randomized subjects returned to the clinic 14 days after randomization (Treatment Phase Study Day 15) but no later than 19 days (Treatment Phase Study Day 20) for study treatment evaluation and collection of Diary card. Subject completed a global evaluation of study drug using six point scales (not effective, poor, fair, good, very good, and excellent) as a treatment for severe heartburn.

The primary efficacy variable was total pain relief (TOTPAR) of severe or very severe heartburn over 2-hour evaluation period for the first study-treated episode. Pain relief was scored on a 7-point (0-6) scale where 0 is no relief and 6 is complete relief. Pain relief was measured at 15 minute intervals over the 2 hour evaluation period. TOTPAR was then measured as a cumulative sum of the eight relief scores. TOTPAR values ranged from 0-48.

The LOCF (Last Observation Carried Forward) methodology was used to replace missing and non-meaningful relief scores (i.e., scores following rescue antacid or re-dosing with study drug). For episodes during which the subject fell sleep, any missing value was replaced with the last previous value. Additionally, if the subject either used rescue antacid or redosed with study medication before the end of the two-hour evaluation period, all values following the rescue or redosing contained the previous value.

The secondary efficacy variables included:

- Subject's overall assessment of study drug efficacy for each episode of severe heartburn
- Subject's global evaluation
- Onset of relief of severe heartburn episodes
- Duration of relief of severe heartburn episodes
- Use of antacid tablets
- Change in Abdominal-Gastric Index of Digestive Annoyance (AGIDA) scores for subjects who treated severe heartburn episodes
- Peak relief of severe heartburn episodes
- Severity of other heartburn episodes over the two week treatment phase
- Number of severe or very severe heartburn episodes over the two week treatment phase
- Relief of nighttime heartburn affecting sleep over the two week treatment phase

The primary statistical comparison was the pairwise comparison of the ranitidine 150mg and ranitidine 75mg. As there was only one primary comparison on one primary endpoint, no multiple comparisons adjustment to p-value was planned.

Pairwise comparisons of the primary efficacy variable, TOTPAR, were performed using the Wilcoxon rank sum test stratified by investigator (i.e., van Elteren test).

These analyses were applied to both the first episode and all episodes. The method for testing secondary comparisons for analyses involving all episodes was Generalized

Estimating Equation (GEE).The method for the first episode analyses was the Wilcoxon rank sum test stratified by investigator (i.e., van Elteren test).

Using alpha=0.05 and power $\geq$ 80%, and assuming a common standard deviation of 11, a sample size of 330 evaluable subjects per arm is sufficient to detect a 2.4-point difference between treatment groups in the TOTPAR scores of the first study-drug-treated episode of severe heartburn.

Two thousand five hundred fifty-four (2,554) adult outpatients participated in the single-blind Run-In Phase of the study. One thousand thirteen (1,013) subjects successfully completed the Run-In Phase, were randomized to treatment, and entered the Treatment Phase of the study (338 ranitidine 75mg, 338 ranitidine 150mg, 337 placebo).

1.2.2 Study RAN3014

This study was a randomized, multicenter (23 sites), double-blind, placebo-controlled, parallel group, ambulatory outpatient study with a single-blind placebo run-in phase for evaluation of ranitidine for the treatment of severe heartburn episodes.

The design of this study was the same as that for the Study RAN3013.

Two thousand fifty-seven (2,057) adult outpatients participated in the single-blind Run-In Phase of the study. One thousand seven (1,007) subjects successfully completed the Run-In Phase, were randomized to treatment, and entered the Treatment Phase of the study (334 ranitidine 75mg, 339 ranitidine 150mg, 334 placebo).

1.3 Statistical Issues and Findings

The sponsor has submitted two controlled efficacy study (RAN3013 and RAN3014) in support of the proposed claim for ranitidine 150mg for treatment of heartburn.

In the protocol, it stated that the primary statistical comparison was the pairwise comparison of the ranitidine 150mg and ranitidine 75mg. As there was only one primary comparison on one primary endpoint, no multiple comparisons adjustment to p-value was planned.

But, Both studies (RAN3013 and RAN3014) showed that there was no statistical significant difference between ranitidine 150mg and ranitidine 75mg in terms of total pain relief (TOTPAR) (p=0.567 in RAN3013 and p=0.980 in RAN3014). For further testing between ranitidine 150mg and placebo and between ranitidine 75mg and placebo, the p-values should be adjusted for multiplicity. To be conservative, the Bonferroni method should be applied. Each of the active treatments was compared to placebo at the an $\alpha/3$ (0.0167) level of significance.

For the pre-specified primary endpoint, total pain relief score (TOTPAR) of severe or very severe heartburn over 2-hour evaluation period for first episode, study RAN3013

showed that there was a statistically significant difference in TOTPAR score between the ranitidine 150mg and placebo for both Intent-to-Treat and efficacy evaluable populations. There was a statistically significant difference in TOTPAR score between the ranitidine 75mg and placebo for the Intent-to-Treat population. For efficacy evaluable population, the treatment difference between ranitidine 75mg and placebo just failed to reach statistical significance level of 0.0167 adjusting for multiple comparisons. The treatment difference of medians between ranitidine 150mg and placebo was 5.0 for both Intent-to-Treat and efficacy evaluable populations.

Study RAN3014 showed that after adjusting for multiple comparisons, there was not statistically significant difference in TOTPAR score between the ranitidine 150mg and placebo groups for both Intent-to-Treat and efficacy evaluable populations. There was not statistically significant difference in TOTPAR score between the ranitidine 75mg and placebo groups for both Intent-to-Treat and efficacy evaluable populations. The treatment difference of medians between ranitidine 150mg and placebo was 2.0 for Intent-to-Treat population.

Both studies (RAN3013 and RAN3014) showed that there was no statistically significant difference between the ranitidine 150mg and ranitidine 75 groups. The treatment differences of medians between ranitidine 150mg and ranitidine 75mg were 2.0 and 1.0, respectively for studies RAN3013 and RAN3014 for Intent-to-Treat population.

For the secondary efficacy endpoints, for total pain relief score (TOTPAR) of severe or very severe heartburn over 2-hour evaluation period for all study drug -treated episodes, study RAN3013 showed that there were statistically significant differences in TOTPAR scores between the ranitidine 150mg and placebo and between ranitidine 75mg and placebo for both Intent-to-Treat and efficacy evaluable populations.

Study RAN3013 revealed that both ranitidine 75mg and ranitidine 150mg groups were more effective than placebo in 3 of 8 secondary efficacy endpoints: subject's overall assessment of study drug efficacy for each episode of severe heartburn, subject's global evaluation, and peak relief of severe heartburn episodes.

For total pain relief score (TOTPAR) of severe or very severe heartburn over 2-hour evaluation period for all study drug -treated episodes, study RAN3014 showed that there were statistically significant differences in TOTPAR scores between the ranitidine 150mg and placebo for the Intent-to-Treat population. For efficacy evaluable population, it just failed to achieve statistical significance level of 0.0167. The ranitidine 75mg was not statistically significantly different from placebo. No statistically significant difference was observed between ranitidine groups.

Study RAN3014 revealed that the ranitidine 150mg group was more effective than placebo in 3 of 8 secondary efficacy endpoints: subject's overall assessment of study drug efficacy for each episode of severe heartburn, subject's global evaluation, and rescue antacid use.

The ranitidine 75mg group was more effective than placebo in 4 of 8 secondary efficacy endpoints: subject's overall assessment of study drug efficacy for each episode of severe heartburn, subject's global evaluation, rescue antacid use and change in AGIDA scores for subjects who treated severe heartburn episodes.

2. INTRUDUCTION

2.1 Overview

Over-the-Counter (OTC) Zantac 75 (Ranitidine 75mg tablet) was approved in December 19, 1995 for relief of heartburn. OTC Zantac 75 was approved in June 8, 1998 for the prevention of heartburn.

In the current NDA, the sponsor seeks approval of the Over-the-Counter (OTC) use of Zantac 150 (Ranitidine Tablet 150 mg) for the treatment of heartburn.

2.2 Data Sources

The sponsor has submitted five Phase III studies: Two trials (RAN3013 and RAN3014) supporting the treatment of heartburn, the other three support prevention of heartburn.

These studies include:

Study RAN3013: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Evaluation of Ranitidine for the Treatment of Severe Heartburn Episodes

Study RAN3014: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Evaluation of Ranitidine for the Treatment of Severe Heartburn Episodes

This review addresses only the treatment of heartburn. Separate review addresses the prevention of heartburn.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study RAN3013

3.1.1.1 Study Design

This study was a randomized, multicenter (23 sites), double-blind, placebo-controlled, parallel group, ambulatory outpatient study with a single-blind placebo Run-In Phase comparing ranitidine 150mg, ranitidine 75mg and placebo in the treatment of severe heartburn episodes. This study was conducted in the US.

The primary objective of this study was to compare the efficacy of ranitidine 150mg to ranitidine 75mg and placebo when taken as needed up to twice daily for two weeks in adults for severe heartburn episodes.

Eligible subjects had the following criteria to participate in this study:

- at least 1 year history of heartburn, sour stomach, or acid indigestion, typically brought on by eating, stress, or postural changes.
- report almost daily heartburn during the two weeks prior to Visit 1 (i.e., at least five of seven days each week in the two weeks prior to Visit 1)
- describe most of their heartburn episodes as being severe or very severe in the two weeks prior to Visit 1 (using the following five-point scale: very mild, mild, moderate, severe, or very severe).

All eligible screened subjects were scheduled for Visit 1. Subjects who qualified entered into the one week Run-In Phase and used single blind study drug (placebo) to treat up to two heartburn episodes (regardless of severity) per day for a period of one week. Maalox was provided to treat heartburn episodes which was not relieved by study drug or were in excess of the two treated by study drug per day.

At Visit 2, those subjects who met the following criteria qualified for participation in the Treatment Phase of the study and were randomized to the double-blind phase of the study for a total of 14 days:

- treated heartburn episodes on at least four of the first seven days during the one week Run-In Phase

- had at least 50% of these episodes rated as severe or very severe (5 point scale: very mild, mild, moderate, severe, and very severe)

Subjects who qualified for entry after the Run-in Phase were randomized to receive either placebo, 75 mg ranitidine, or 150 mg ranitidine, for up to twice daily use, for a total of 14 days, for the treatment of severe or very serve heartburn episodes.

Subjects took the study drug as needed to treat up to two severe or very severe episodes per day. They were also given rescue antacid of Maalox.

Subject was instructed to take the study drug as follows:

- Subject might treat up to two severe or very severe heartburn episodes per day.
- Subject might only take one dose of study drug to treat each heartburn episode considered by the subject to be severe or very severe.
- Subject might not take more than two doses of study drug in any calendar day.
- For severe or very severe heartburn episodes that were not relieved by the study drug, subject should take the supplied rescue antacid, beginning two hours after ingesting study drug, until that heartburn episode was relieved.

- If the heartburn episode was not considered by the subject to be severe or very severe, the subject should take the supplied rescue antacid tablets, i.e., chewed 1-2 tablets and repeated as needed until that episode of heartburn was relieved.
- If antacid tablets were used to treat a non-severe heartburn episode, under no circumstances might study drug be used to later treat that same episode.
- Subject might not treat a new episode of severe or very severe heartburn with another dose of study drug until the previous heartburn episode had been relieved and at least two hours had elapsed since the previous dose of study drug was taken.
- If a subject had a second severe or very severe heartburn episode at least 2 hours following the ingestion of the first dose of study drug for that day, the subject might ingest the second and final dose of study drug for the calendar day for the treatment of this episode.
- If a subject had treated two severe or very severe heartburn episodes in a calendar day with study drug, all other heartburn episodes regardless of severity might only be treated with only the supplied rescue antacids.

Subjects completed a Diary to assess the severity of all heartburn episodes for each day of the Treatment Phase and heartburn relief for two hours following treatment with study drug for severe or very severe heartburn episodes. Subject completed an overall assessment of study drug efficacy using 6 point scales (not effective, poor, fair, good, very good, and excellent) for each episode of severe or very severe heartburn treated with study drug. Each morning subjects assessed if nighttime heartburn interfered with their sleep with yes/no.

All randomized subjects returned to the clinic 14 days after randomization (Treatment Phase Study Day 15) but no later than 19 days (Treatment Phase Study Day 20) for study treatment evaluation and collection of Diary card. Subject completed a global evaluation of study drug using six point scales (not effective, poor, fair, good, very good, and excellent) as a treatment for severe heartburn.

The primary efficacy variable was total pain relief (TOTPAR) of severe or very severe heartburn over 2-hour evaluation period for the first study-treated episode. Pain relief was scored on a 7-point (0-6) scale where 0 is no relief and 6 is complete relief. Pain relief was measured at 15 minute intervals over the 2 hour evaluation period. TOTPAR was then measured as a cumulative sum of the eight relief scores. TOTPAR values ranged from 0-48.

The LOCF (Last Observation Carried Forward) methodology was used to replace missing and non-meaningful relief scores (i.e., scores following rescue antacid or re-dosing with study drug). For episodes during which the subject fell sleep, any missing value was replaced with the last previous value. Additionally, if the subject either used rescue antacid or redosed with study medication before the end of the two-hour evaluation period, all values following the rescue or redosing contained the previous value.

The secondary efficacy variables included:

- Subject's overall assessment of study drug efficacy for each episode of severe heartburn
- Subject's global evaluation
- Onset of relief of severe heartburn episodes
- Duration of relief of severe heartburn episodes
- Use of antacid tablets
- Change in Abdominal-Gastric Index of Digestive Annoyance (AGIDA) scores for subjects who treated severe heartburn episodes
- Peak relief of severe heartburn episodes
- Severity of other heartburn episodes over the two week treatment phase
- Number of severe or very severe heartburn episodes over the two week treatment phase
- Relief of nighttime heartburn affecting sleep over the two week treatment phase

Using alpha=0.05 and power $\geq$ 80%, and assuming a common standard deviation of 11, a sample size of 330 evaluable subjects per arm is sufficient to detect a 2.4-point difference between treatment groups in the TOTPAR scores of the first study-drug-treated episode of severe heartburn.

The original protocol was amended three times.

Amendment 01 (October 31, 1996) modified the study protocol inclusion criteria as follows:

- In order to consistent with all previous studies and to reduce confusion, the prestudy heartburn, sour stomach, or acid indigestion history requirement was modified from "at least 1 year' to 'at least a 6 months'.

- To ensure that eligibility requirements were consistent between the Run-In and Treatment Phases, the requirement for heartburn frequency during the 2 weeks prior to Visit 1 was changed from 'at least 5 of the 7 days each week' to 'at least 4 of the 7 days each week'.

Amendment 02 (November 22,1996) modified the study protocol randomization criteria as follows:

- In order to allow for a full 7 days of evaluation, the required number of days that subjects treated a heartburn episode or had at least 50% of their heartburn episode recorded on the diary card was modified from 'at least 4 of the first 7 days of the 1-week Run-In Phase' to 'at least 4 of the first 8 days of the Run-In Phase'.

- An option was added regarding the way that subjects could qualify for randomization based upon the heartburn experienced during the Run-In Phase. Rather than only evaluating the number of severe or very severe episodes (i.e., at least 50% of the heartburn episodes recorded on the diary during the first 8 days of the Run-In Phase should be rated as severe or very severe) the option to have a severe or very severe episode on at least 4 days during the first 8 days of the Run-In Phase was added.

Amendment 03 (February 13,1997) modified prospectively the study protocol statistical analyses as follows:

- For all analyses using pain relief scores, for episodes during which the subject fell asleep, any missing values were replaced with the last non-missing value. Additional, if the subject either used rescue antacid or redosed with study medication before the end of a 2-hour evaluation period, all values following the rescue or redosing contained the previous value. The original protocol stated that this method was used only for primary efficacy measurements, however, it was always the sponsor's intention to use this method for all pain relief score analyses.

- Change the pairwise comparisons of mean heartburn relief scores to include each timepoint over the 2-hour heartburn episode evaluation period for each study drug-treated severe or very severe episode. In the original protocol, it was stated that this analysis was performed at 15, 30, and 45 minutes after the start of each study drug-treated severe heartburn and that the values used at each timepoint was the lower of the scores at that timepoint and the immediately following timepoint. This was changed because in the sponsor's opinion, it was important to look at each timepoint over the 2-hour heartburn episode evaluation period and to use the raw scores at each timepoint.

- In the calculation of 'duration of relief', the beginning of relief was redefined as the first time at which a subject gave a rating of at least 'Little Relief' and cessation of relief was redefined as the first time a subject rescued with antacid, redosed with study medication, or gave a lower rating than 'Little Relief'. The sponsor considered this to be a more straightforward way of analyzing these data.

- A new analysis, 'relief of severe or very severe heartburn episodes at each timepoint over the 2-hour heartburn episode assessment period' was added. In the sponsor's opinion, it was beneficial to examine the proportion of subjects achieving a given level of relief at each timepoint as an additional secondary endpoint to evaluate those subjects who achieved any relief as well as those who achieved complete relief.

3.1.1.2 Sponsor's Analysis

Two thousand five hundred fifty-four (2,554) adult outpatients participated in the single-blind Run-In Phase of the study. One thousand thirteen (1,013) subjects successfully completed the Run-In Phase, were randomized to treatment, and entered the Treatment Phase of the study (338 ranitidine 75mg, 338 ranitidine 150mg and 337 placebo).

Among 1,013 randomized subjects, 976 subjects completed the study (327 in ranitidine 75mg, 326 in ranitidine 150mg, and 323 in placebo). The most common reason for discontinuation was "lost to follow-up."

A total of 257 subjects (84 in ranitidine 75mg. 88 in ranitidine 150mg and 85 in placebo) violated the study protocol during the trial. The most commonly-occurring protocol violation was "drug accountability problems."

Among 15,124 episodes (5,216 in ranitidine 75mg, 5,146 in ranitidine 150mg, and 4,762 in placebo), 1,460 episodes (547 in ranitidine 75mg, 461 in ranitidine 150mg, and 452 in placebo) had protocol violations. The most common reason that episodes were deemed unevaluable was "eating or drinking during an episode."

Of 1,013 randomized subjects, 969 reported at least one episode of heartburn (326 in ranitidine 75mg, 321 in ranitidine 150mg, and 322 in placebo). Of the 969 subjects who reported at least one episodes of heartburn, 956 rated their first heartburn episode as severe or very serve (323 in ranitidine 75mg, 313 in ranitidine 150mg, and 320 in placebo).

3.1.1.2.1 Planned Analysis

The primary statistical comparison was the pairwise comparison of the ranitidine 150mg and ranitidine 75mg. As there was only one primary comparison on one primary endpoint, no multiple comparisons adjustment to p-value was planned.

Pairwise comparisons of the primary efficacy variable, TOTPAR, were performed using the Wilcoxon rank sum test stratified by investigator (i.e., van Elteren test).

These analyses were applied to both the first episode and all episodes. The method for testing secondary comparisons for analyses involving all episodes was Generalized Estimating Equation (GEE).The method for the first episode analyses was the Wilcoxon rank sum test stratified by investigator (i.e., van Elteren test).

The "All subject" population consisted of all subjects enrolled in the study. Subjects who were randomized formed the "Intent-to-Treat" population. Subjects were identified as part of the "Efficacy Evaluable" population if they passed all inclusion and exclusion criteria, took study medication according to the protocol, abided by all protocol instructions and provided sufficient heartburn diary assessments to evaluate a given efficacy parameter.

All summaries and statistical comparisons of efficacy were based upon the "Intent-to-Treat" population with the exception of two TOTPAR analyses (first and all episodes), for which an Efficacy Evaluable subset of subjects was used (N=686).

3.1.1.2.2 Treatment Group Comparability

A summary of the number of patients by baseline characteristics by treatment group is given in Appendix Table 1.

As seen from Appendix Table 1, the treatment groups appeared similar with regard to all baseline characteristics with one exception. Mean age were higher in placebo group as compared to ranitidine groups (42.8 vs. 40.8).

3.1.1.2.3 Sponsor's Analysis of Primary Efficacy Variable

The primary efficacy variable was total pain relief (TOTPAR) of severe or very severe heartburn over 2-hour evaluation period for the first study-treated episode. Pain relief was be scored on a 7-point (0-6) scale where 0 is no relief and 6 is complete relief. Pain relief was measured at 15 minute intervals over the 2 hour evaluation period. TOTPAR was then measured as a cumulative sum of the eight relief scores. TOTPAR values ranged from 0-48.

The LOCF (Last Observation Carried Forward) methodology was used to replace missing and non-meaningful relief scores (i.e., scores following rescue antacid or re-dosing with study drug) with the following adjustments. If the subject fell asleep or did not record a relief score within the two-hour assessment period, then the most-immediately-preceding relief score was carried forward into the missing scores. If however, the subject missed the first pain relief score, then all relief scores were set to missing and no scores were imputed. If additional medication occurred prior to the first relief score, then scores of 0 ("No Relief") were imputed into all 8 pain relief scores.

The results for the analysis of primary efficacy parameter are given below. Subjects were excluded from this analysis if their first Treatment Phase episode was not rated as being severe or very severe.

Total Pain Relief (TOTPAR) Score for First Episode
Protocol RAN3013
Intent-to-Treat Population

Treatment	N	Mean	(SD)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	323	20.1	(0.72)	19.0	0.015	
Ranitidine 150mg	313	20.6	(0.72)	21.0	0.005	0.567
Placebo	320	17.5	(0.69)	16.0		

Copied from Table 17.
P-values were calculated using the Wicoxon Rank Sum test stratified by investigator (i.e., van Elteren).

As seen from table above, TOTPAR score was higher in both ranitidine 75mg and ranitidine 150mg groups as compared to the placebo group. Comparison of the TOTPAR scores revealed no statistically significant difference between the ranitidine 150mg and the ranitidine 75mg treatment groups.

3.1.1.2.4 Sponsor's Analysis of Secondary Efficacy Variable

3.1.1.2.4.1 TOTPAR Scores across All Study Drug-Treated Heartburn Episodes

The TOTPAR scores across all study drug-treat heartburn episodes that were rated as severe or very severe by treatment groups are summarized below.

Total Pain Relief (TOTPAR) Score for All Episodes
Protocol RAN3013
Intent-to-Treat Population

Treatment	N	Mean	(SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	338	18.9	(0.17)	18.0	0.003	
Ranitidine 150mg	338	19.5	(0.18)	18.0	<0.001	0.495
Placebo	337	16.3	(0.18)	15.0		

Copied from Table 17.01.
P-values were calculated using Generalized Estimating Equations.

As seen from table above, for the TOTPAR scores for all episodes, both ranitidine 75mg and ranitidine 150mg groups were statistically significantly higher than the placebo group. There was no significant difference in TOTPAR scores between the two ranitidine treatments.

3.1.1.2.4.2 TOTPAR Scores of the Efficacy Evaluable Episodes

The TOTPAR scores of efficacy evaluable episodes for the first episode and all episodes are summarized in below.

Total Pain Relief (TOTPAR) Score
Protocol RAN3013
Efficacy Evaluable Population

First Episode

Treatment	N	Mean	(SD)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	231	20.4	(12.9)	20.0	0.019	
Ranitidine 150mg	231	20.5	(12.7)	20.0	0.017	0.641
Placebo	230	17.6	(12.3)	15.0		

Copied from Table 17.12.
P-values were calculated using the Wicoxon Rank Sum test stratified by investigator (i.e., van Elteren).

All Episodes

Treatment	N	Mean	(SD)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	231	19.1	(12.9)	18.0	0.016	
Ranitidine 150mg	231	19.5	(12.7)	18.0	0.007	0.775
Placebo	230	16.7	(12.3)	15.0		

Copied from Table 17.12.
P-values were calculated using the Generalized Estimating Equations.

As seen from table above, TOTPAR score was higher in both ranitidine 75mg and ranitidine 150mg groups as compared to the placebo group for both first episode and all episodes. The treatment difference between ranitidine 75mg and placebo just failed to reach statistical significance at significance level of 0.0167 for adjusting for multiple comparisons for first episode. Comparison of the TOTPAR scores revealed no statistically significant difference between the ranitidine 150mg and the ranitidine 75mg treatment groups.

3.1.1.2.4.3 Subject's Overall Assessment of Study Drug Efficacy for Each Episode of Severe Heartburn

Summary of subject's overall assessment of study drug efficacy for each severe heartburn episode is given below. This evaluation was performed at the end of each study-drug treated episode.

Summary of Subject Overall Episode Evaluation for Each Severe or Very Severe Episode During Treatment Phase
Protocol RAN3013
Intent-to-Treat Population

First Episode

	Ranitidine 75mg N=338	Ranitidine 150mg N=338	Placebo N=337
First Episode: Number of episodes	323	315	320
0=Not effective	25 (8%)	14 (4%)	29 (9%)
1=Poor	42 (13%)	46 (15%)	57 (18%)
2=Fair	68 (21%)	60 (19%)	91 (28%)
3=Good	98 (30%)	92 (29%)	82 (26%)
4=Very good	63 (20%)	71 (23%)	44 (14%)
5=Excellent	24 (7%)	28 (9%)	15 (5%)
Unknown	3 (<1%)	4 (1%)	2 (<1%)
Comparison with Placebo	0.002	<0.001	
Comparison with Ranitidine 75 mg		0.215	

Copied from Table 19.
P-values were calculated using Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

All Episodes

	Ranitidine 75mg N=338	Ranitidine 150mg N=338	Placebo N=337
All Episode: Number of episodes	5102	5093	4724
0=Not effective	337 (7%)	281 (6%)	504 (11%)
1=Poor	645 (13%)	522 (10%)	801 (17%)
2=Fair	1030 (20%)	1170 (23%)	1162 (25%)
3=Good	1415 (28%)	1398 (27%)	1176 (25%)
4=Very good	1077 (21%)	1124 (22%)	796 (17%)
5=Excellent	510 (10%)	519 (10%)	212 (4%)
Unknown	88 (2%)	79 (2%)	73 (2%)
Comparison with Placebo	<0.001	<0.001	
Comparison with Ranitidine 75 mg		0.390	

Copied from Table 19.
P-values were calculated using Generalized Estimating Equation with investigator in the model.

As seen from tables above, for treating the first study drug-treated heartburn episode, both ranitidine 75mg and ranitidine 150mg groups were more effective than the placebo

group. Comparison of the treatment groups revealed no significant difference between the ranitidine 150mg and the ranitidine 75mg groups.

For treating all of severe and very severe heartburn episodes, both ranitidine 75mg and ranitidine 150mg groups were more effective than the placebo group. No significant difference between the ranitidine groups was detected.

3.1.1.2.4.4 **Subject's Global Evaluation**

The result of analysis of subject's global evaluation at end of Treatment Phase is given below.

Summary of Subject's Global Evaluation at End of Treatment Phase
Protocol RAN3013
Intent-to-Treat Population

	Ranitidine 75mg N=338	Ranitidine 150mg N=338	Placebo N=337
Subjects with Global Evaluation	328	328	323
Subject's Global Evaluation			
0=Not effective	16 (5%)	11 (3%)	23 (7%)
1=Poor	43 (13%)	29 (9%)	53 (16%)
2=Fair	55 (17%)	59 (18%)	78 (24%)
3=Good	104 (32%)	106 (32%)	98 (30%)
4=Very good	83 (25%)	96 (29%)	65 (20%)
5=Excellent	25 (8%)	20 (6%)	5 (2%)
Unknown	2 (<1%)	7 (2%)	1 (<1%)
Comparison with Placebo	<0.001	<0.001	
Comparison with Ranitidine 75 mg		0.144	

Copied from Table 20
Correction was made in Adjustment to Clinical Report.
P-values were calculated using Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

As seen from table above, for the subject's global evaluation of the study drug as a treatment for severe heartburn, both ranitidine 75mg and ranitidine 150mg groups were more effective than the placebo group. Comparison of the treatment groups revealed no significant difference between the ranitidine 150mg and the ranitidine 75mg groups.

3.1.1.2.4.5 **Onset of Relief of Severe Heartburn Episodes**

The LOCFed pain relief scores were summarized by treatment group at 15 minutes, 30 minutes, 45 minutes, 1 hour, 1 hour 15 minutes, 1 hour 30 minutes, 1 hour 45 minutes, and 2 hours after study drug for severe heartburn episodes. For the First Episode, pairwise comparisons of the treatment groups at assessment timepoint were performed using a Wilcoxon rank sum test stratified by investigator (i.e., van Elteren test). For All Episodes, comparisons between the treatment groups were performed using Generalized Estimating Equation techniques.

Summaries of the LOCFed pain relief scores for the first study drug-treated episode at 15 minutes, 30 minutes, 45 minutes, 1 hour, 1 hour 15 minutes, 1 hour 30 minutes, 1 hour 45 minutes, and 2 hours after dosing in Appendix Tables 2 to 9, respectively.

As seen from Appendix Tables 2 to 9, at 15 minutes after study drug dosing, none of the treatment groups differed in their experience of pain relief. At 30 minutes after study drug dosing, the number of subjects experiencing complete relief was statistically greater in the ranitidine 150mg group (13/315; 4%) than in placebo group (3/320; <1%) (p=0.011). At one hour, both the ranitidine 150mg group (41/315, 13%) and the ranitidine 75mg group (46/323, 14%) had significantly greater proportion of subjects with complete relief than did the placebo group (25/320, 8%) (p=0.029 and p=0.012, respectively). At no time was there a statistically significant difference between the two ranitidine treatment groups.

3.1.1.2.4.6 **Duration of Relief of Severe Heartburn Episodes**

Duration of relief was computed as the number of hours between the first LOCFed pain relief score of at least "Little Relief" until the earliest time at which the subject re-dosed with study medication, used any antacid, or reported "No Relief." For the first severe episode analysis, treatment group comparisons were performed using an analysis of variance model with an investigator term.

The summary of duration (hours) of relief for both the first study drug-treated episode and across all study drug-treated episodes is given below.

Summary of Duration (Hours) of Relief
Protocol RAN3013
Intent-to-Treat Population

First Episode

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	318	13.1 (1.09)	7.1	0.604	
Ranitidine 150mg	313	15.7 (1.19)	9.8	0.025	0.086
Placebo	319	12.3 (0.97)	4.8		

Copied from Table 22.
P-values were calculated using analysis of variance stratified by investigator.

All Episodes

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	4759	10.4 (0.20)	6.4	0.277	
Ranitidine 150mg	4753	10.9 (0.19)	7.0	0.040	0.321
Placebo	4399	9.6 (0.21)	3.8		

Copied from Table 22.
P-values were calculated using Generalized Estimating Equation with investigator in the model.

As seen from tables above, for the first study drug-treated episode, mean duration of relief for ranitidine 150mg group was numerically longer than that of the placebo group. It did not achieved statistical significance at significance level of 0.0167 for adjusting for multiple comparisons. The ranitidine 75mg was not statistically different from placebo. The duration of relief for the two ranitidine treatment groups was not significantly different.

For all study drug-treated episodes, the ranitidine 150mg group experienced a duration of relief which was numerically longer than that of the placebo group. It did not achieve statistical significance at significance level of 0.0167 for adjusting for multiple comparisons. The ranitidine 75mg was not statistically different from placebo. The ranitidine 150mg group did not differ significantly from ranitidine 75mg group.

3.1.1.2.4.7 **Rescue Antacid Use**

The definition of rescue antacid use was refined to consider antacid use identified on either the study drug treated or the non-study drug treated heartburn episode diary pages. Subjects who used any antacid within three hours of ingesting the study drug were considered to have used rescue antacid. Number and proportion of subjects who used rescue antacid for a study drug-treated heartburn episode were summarized by treatment group. In the first severe episode analysis, treatment group comparisons were performed using a Cochran-Mantel-Haenszel test stratified by investigators.

Summary of rescue antacid use is given below.

Summary of Rescue Antacid Use
Protocol RAN3013
Intent-to-Treat Population

First Episode

Treatment	Used Antacid	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	100/323 (31%)	0.763	
Ranitidine 150mg	77/315 (24%)	0.028	0.051
Placebo	103/320 (32%)		

Copied from Table 23.
Correction was made in Adjustment to Clinical Report.
P-values were calculated using Mantel-Haenszel test stratified by investigator.

All Episodes

Treatment	Used Antacid	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	1647/5102 (32%)	0.003	
Ranitidine 150mg	1503/5093 (30%)	<0.001	0.243
Placebo	1926/4724 (41%)		

Copied from Table 23.
Correction was made in Adjustment to Clinical Report.
P-values were calculated using General Estimating Equations with investigator in the model.

As seen from tables above, for the first study drug-treated heartburn episode, numerically smaller proportion of subjects in the ranitidine 150mg treatment group utilized rescue antacid as compared to the placebo group. But, it did not achieve statistical significance at significance level of 0.0167 for adjusting for multiple comparisons. The ranitidine 75mg was not statistically different from placebo. There was a non-statistical smaller percentage of subjects in the ranitidine 150mg group who used rescue antacid as compared to the ranitidine 75mg group.

For all drug-treated episodes, both ranitidine 75mg and ranitidine 150mg groups had a statistically significant smaller proportion of episodes rescued with antacid as compared to the placebo group. There was no significant difference between the two ranitidine groups.

3.1.1.2.4.8 **Change in Abdominal-Gastric Index of Digestive Annoyance (AGIDA) Scores for Subjects Who Treated Severe Heartburn Episodes**

Summary of Change in AGIDA scores for severe heartburn is given in Appendix Table 10.

As seen from Appendix Table 10, there were no differences between any of the treatment groups in their changes in Total AGIDA scores.

3.1.1.2.4.9 **Peak Relief of Severe Heartburn Episode**

Number and proportion of subjects in each ordinal category of peak relief heartburn episodes were summarized by treatment group. Mean and median peak values were also summarized by treatment group and treatment group comparisons were performed using a Wilcoxon rank sum test stratified by investigator (i.e., van Elteren test).

Summary of the peak pain relief scores for the first study-treated heartburn episode is given below.

Summary of First Episode: Peak Relief Score of Severe or Very Severe Heartburn Episode
Protocol RAN3013
Intent-to-Treat Population

	Ranitidine 75mg N=338	Ranitidine 150mg N=338	Placebo N=337
First Episode Rated Severe or Very Severe	323	313	320
Peak Relief Score			
0=No Relief	25 (8%)	14 (4%)	28 (9%)
1=Little Relief	31 (10%)	36 (12%)	41 (13%)
2=Some Relief	38 (12%)	42 (13%)	45 (14%)
3=Moderate Relief	44 (14%)	27 (9%)	46 (14%)
4=Considerate Relief	29 (9%)	38 (12%)	39 (12%)
5=Almost Complete Relief	39 (12%)	43 (14%)	38 (12%)
6=Complete Relief	117 (36%)	113 (36%)	83 (26%)
Mean of peak relief scores	3.9	4.0	3.5
Median of peak relief scores	4.0	4.0	3.5
Comparison with Placebo	0.016	0.001	
Comparison with Ranitidine 75mg		0.658	

Copied from Table 26.
P-values were calculated using Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

As seen from table above, for the first study drug-treated heartburn episode, both ranitidine 75mg and ranitidine 150mg groups experienced a higher peak relief score than did the placebo group. The ranitidine 150mg did not differ from the ranitidine 75mg group.

3.1.1.2.4.10 Severity of Other Heartburn Episodes over the Two Week Treatment Phase

Summary of the number of non-study drug-treated heartburn episodes is given in Appendix Table 11.

As seen from Appendix Table 11, during the two weeks of the Treatment Phase, the ranitidine 150mg group had a higher mean number of non-study drug-treated episodes compared with the placebo group.

3.1.1.2.4.11 Relief of Nighttime Heartburn Affect Sleep over the Two Week Treatment Phase

Summary of relief of nighttime heartburn affecting sleep during Treatment Phase is given in Appendix Table 12.

As seen from Appendix Table 12, a slightly larger proportion of subjects in the placebo group experiencing either awakening from sleep or prevention of sleep due to heartburn symptoms (23%) as compared to the ranitidine 150mg group (19%, p=0.040). But, it failed to achieve statistical significance at significance level of 0.0167 for adjusting for

multiple comparisons. The ranitidine 75mg was not statistically different from placebo. No differences in nighttime heartburn were detected between the ranitidine 75mg group and the ranitidine 150mg group.

3.1.1.3 Reviewer's Comments and Evaluation

3.1.1.3.1 Multiplicity Issue

In the protocol, it stated that the primary statistical comparison was the pairwise comparison of the ranitidine 150mg and ranitidine 75mg. As there was only one primary comparison on one primary endpoint, no multiple comparisons adjustment to p-value was planned.

But, this study showed that there was no statistically significant difference between ranitidine 150mg and ranitidine 75mg in terms of total pain relief (TOTPAR) ($p=0.567$). For further testing between ranitidine 150mg and placebo and between ranitidine 75mg and placebo, the p-values should be adjusted for multiplicity. To be conservative, the Bonferroni method should be applied. Each of the active treatments was compared to placebo at the an $\alpha/3$ (0.0167) level of significance.

3.1.1.3.2 LOCF Analyses

The sponsor used the LOCF (last observation carried forward) method to replace missing and non-meaningful relief scores (i.e., scores following rescue antacid or re-dosing with study drug) in both analysis of primary efficacy endpoint and analyses of secondary efficacy endpoints. It is not clear whether the LOCF analysis would provides robust results. Sensitivity analysis should be carried out.

3.1.1.3.3 Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Endpoint

3.1.1.3.3.1 TOTPAR Scores for First Episode

For the pre-specified primary endpoint, total pain relief score (TOTPAR) of severe or very severe heartburn over 2-hour evaluation period for first episode, it was shown that there was a statistically significant difference in TOTPAR score between the ranitidine 150mg and placebo for both Intent-to-Treat and efficacy evaluable populations. There was a statistically significant difference in TOTPAR score between the ranitidine 75mg and placebo for the Intent-to-Treat population. For efficacy evaluable population, the treatment difference between ranitidine 75mg and placebo just failed to reach statistical significance level of 0.0167 adjusting for multiple comparisons. The treatment difference of medians between ranitidine 150mg and placebo was 5.0 for both Intent-to-Treat and efficacy evaluable populations.

There was no statistically significant difference between the ranitidine 150mg and ranitidine 75 groups. The treatment difference of medians between ranitidine 150mg and ranitidine 75mg was 2.0 for Intent-to-Treat population.

3.1.1.3.3.2 Subgroup Analysis

The sponsor also performed subgroup analyses of the primary efficacy endpoint by race (white vs. non white), gender, and age (<65 vs. ≥65). The results for subgroup analyses are given below.

Total Pain Relief (TOTPAR) Scores for First Episode by Subgroup
Protocol RAN3013
Intent-to-Treat Population

Subgroup	Ranitidine 75mg N	Mean	Median	Ranitidine 150mg N	Mean	Median	Placebo N	Mean	Median	Ran 75mg vs Placebo P-value	Ran 150mg vs. Placebo P-value	Ran 75mg vs. Ran 150mg P-value
Race												
White	259	20.0	20.0	262	20.3	19.5	262	17.5	16.0	0.048	0.019	0.640
Non-White	64	20.5	19.0	51	21.8	21.0	58	17.5	15.5	0.857	0.208	0.933
Gender												
Male	167	21.7	21.0	167	21.4	21.0	155	18.0	16.0	0.077	0.030	0.887
Female	156	18.5	18.0	146	19.7	19.0	165	17.0	15.0	0.568	0.188	0.584
Age												
<65	315	20.1	19.0	298	20.2	20.0	303	17.5	16.0	0.016	0.010	0.827
≥65	8	21.0	19.5	15	28.0	30.0	17	17.7	20.0	0.330	0.943	0.321
Tobacco User												
Yes	102	18.5	19.0	108	19.6	19.0	96	16.1	13.0	0.241	0.065	0.720
No	221	20.9	19.0	205	21.0	21.0	224	18.1	17.0	0.083	0.012	0.770
Maximum two doses												
Yes	31	14.4	14.0	26	17.0	17.0	19	11.9	10.0	0.245	0.484	0.330
No	292	20.7	20.0	287	20.9	21.0	301	17.9	16.0	0.014	0.006	0.615

Copied from Tables 17.02-17.11.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

As seen from table above, male subjects had higher TOTAP score for first episode than female subjects. Ranitidine 150mg group was more effective than placebo for subjects age <65 and subjects with maximum doses less than two. Superiority of ranitidine 150mg versus placebo was not consistent across race, gender, tobacco user, and subject with maximum two doses.

3.1.1.3.4 Reviewer's Comments on Sponsor's Analysis of Secondary Efficacy Endpoints

For total pain relief score (TOTPAR) of severe or very severe heartburn over 2-hour evaluation period for all study drug-treated episodes, it was shown that there were statistically significant differences in TOTPAR scores between the ranitidine 150mg and placebo and between ranitidine 75mg and placebo for both Intent-to-Treat and efficacy evaluable populations.

This study revealed that both ranitidine 75mg and ranitidine 150mg groups were more effective than placebo in 3 of 8 secondary efficacy endpoints: subject's overall assessment of study drug efficacy for each episode of severe heartburn, subject's global evaluation, and peak relief of severe heartburn episodes.

3.1.2 **Study RAN3014**

3.1.2.1 **Study Design**

This study was a randomized, multicenter (23 sites), double-blind, placebo-controlled, parallel group, ambulatory outpatient study with a single-blind placebo run-in phase for evaluation of ranitidine for the treatment of severe heartburn episodes.

The design of this study was the same as that for the Study RAN3013.

3.1.1.3 Sponsor's Analysis

Two thousand fifty-seven (2,057) adult outpatients participated in the single-blind Run-In Phase of the study. One thousand seven (1,007) subjects successfully completed the Run-In Phase, were randomized to treatment, and entered the Treatment Phase of the study (334 ranitidine 75mg, 339 ranitidine 150mg, and 334 placebo).

Among 1,007 randomized subjects, 977 subjects completed the study (326 in ranitidine 75mg, 329 in ranitidine 150mg, and 322 in placebo). The most common reason for discontinuation was "lost to follow-up."

A total of 262 subjects (74 in ranitidine 75mg. 93 in ranitidine 150mg and 95 in placebo) violated the study protocol during the trial. The most commonly-occurring protocol violation was "drug accountability problems."

Among 14,599 episodes (4,898 in ranitidine 75mg, 5,013 in ranitidine 150mg, and 4,688 in placebo), 1,710 episodes (533 in ranitidine 75mg, 604 in ranitidine 150mg, and 573 in placebo) had protocol violations. The most common reason that episodes were deemed unevaluable was "eating or drinking during an episode."

All summaries and statistical comparisons of efficacy were based upon the "Intent-to-Treat" population with the exception of two TOTPAR analyses (first and all episodes), for which an Efficacy Evaluable subset of subjects was used (N=745).

Of 1,007 randomized subjects, 969 reported at least one episode of heartburn (322 in ranitidine 75mg, 328 in ranitidine 150mg, and 319 in placebo). Of the 969 subjects who reported at least one episodes of heartburn, 952 rated their first heartburn episode as severe or very serve (313 in ranitidine 75mg, 324 in ranitidine 150mg, and 315 in placebo).

3.1.1.3.1 Planned Analysis

The planned analysis of this study was the same as that for the Study RAN3013.

3.1.1.3.2 Treatment Group Comparability

A summary of the number of patients by baseline characteristics by treatment group is given in Appendix Table 13.

As seen from Appendix Table 13, the treatment groups appeared similar with regard to all baseline characteristics with two exceptions. More ranitidine subjects (50% for ranitidine 75mg and 53% for ranitidine 150mg) than placebo subjects (42%) reported that they ever saw a doctor because of heartburn, sour stomach or acid indigestion. Number of days ranitidine subjects experienced heartburn over the last week and over the week before was higher as compared to placebo subjects.

3.1.1.3.3 Sponsor's Analysis of Primary Efficacy Variable

The primary efficacy variable was total pain relief (TOTPAR) of severe or very severe heartburn over 2-hour evaluation period for the first study-treated episode. Pain relief would be scored on a 7-point (0-6) scale where 0 is no relief and 6 is complete relief. Pain relief was measured at 15 minute intervals over the 2 hour evaluation period. TOTPAR was then measured as a cumulative sum of the eight relief scores. TOTPAR values ranged from 0-48.

The LOCF (Last Observation Carried Forward) methodology was used to replace missing and non-meaningful relief scores (i.e., scores following rescue antacid or re-dosing with study drug) with the following adjustments. If the subject fell asleep or did not record a relief score within the two-hour assessment period, then the most-immediately-preceding relief score was carried forward into the missing scores. If however, the subject missed the first pain relief score, then all relief scores were set to missing and no scores were imputed. If additional medication occurred prior to the first relief score, then scores of 0 ("No Relief") were imputed into all 8 pain relief scores.

The results for the analysis of primary efficacy parameter are given below. Subjects were excluded from this analysis if their first Treatment Phase episode was not rated as being severe or very severe.

Total Pain Relief (TOTPAR) Score for First Episode
Protocol RAN3014
Intent-to-Treat Population

Treatment	N	Mean	(SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	313	20.7	(0.70)	21.0	0.093	
Ranitidine 150mg	324	21.1	(0.68)	20.0	0.042	0.980
Placebo	315	19.1	(0.73)	18.0		

Copied from Table 17.
P-values were calculated using the Wicoxon Rank Sum test stratified by investigator (i.e., van Elteren).

As seen from table above, ranitidine 150mg did not achieve statistical significance when compared to placebo at significance level of 0.0167 for adjusting for multiple comparisons. There was no statistically significant difference between ranitidine 75mg and placebo. Comparison of the TOTPAR scores revealed no statistically significant difference between the ranitidine 150mg and the ranitidine 75mg treatment groups.

3.1.2.2.4 Sponsor's Analysis of Secondary Efficacy Variable

3.1.2.2.4.1 TOTPAR Scores across All Study Drug-Treated Heartburn Episodes

The TOTPAR scores across all study drug-treat heartburn episodes that were rated as severe or very severe by treatment groups are summarized below.

Total Pain Relief (TOTPAR) Score for All Episodes
Intent-to-Treat Population

Protocol RAN3014

Treatment	N	Mean	(SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	334	19.5	(0.18)	20.0	0.139	
Ranitidine 150mg	339	20.2	(0.17)	19.0	0.011	0.245
Placebo	334	17.9	(0.19)	17.0		

Copied from Table 17.01.
P-values were calculated using Generalized Estimating Equations .

As seen from table above, for the total pain relief scores for all episodes, the ranitidine 150mg achieved statistical significance when compared to placebo at significance level of 0.0167 for adjusting for multiple comparisons. There was no statistically significant difference between ranitidine 75mg and placebo. There was no significant difference in TOTPAR scores between the two ranitidine treatment groups.

3.1.2.2.4.2 TOTPAR Scores of the Efficacy Evaluable Episodes

The TOTPAR scores of efficacy evaluable episodes for the first and all episodes are summarized in below.

Total Pain Relief (TOTPAR) Score
Protocol RAN3014
Efficacy Evaluable Population

First Episode

Treatment	N	Mean	(SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	234	20.6	(0.82)	20.0	0.176	
Ranitidine 150mg	222	20.5	(0.83)	20.0	0.180	0.893
Placebo	214	18.8	(0.89)	18.0		

Copied from Table 17.12.
P-values were calculated using the Wicoxon Rank Sum test stratified by investigator (i.e., van Elteren).

All Episodes

Treatment	N	Mean	(SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	234	19.2	(0.21)	19.0	0.185	
Ranitidine 150mg	222	20.0	(0.21)	19.0	0.031	0.308
Placebo	214	17.9	(0.23)	17.0		

Copied from Table 17.12.
P-values were calculated using the Generalized Estimating Equations..

As seen from table above, in the First Episode analysis, the ranitidine 150mg group was not statistically significant different from placebo. In the All Episodes analysis, the ranitidine 150mg failed to achieve statistical significance when compared to placebo at significance level of 0.0167 for adjusting for multiple comparisons. There was no statistically significant difference between ranitidine 75mg and placebo. There was no significant difference in TOTPAR scores between the two ranitidine treatment groups.

3.1.2.2.4.3 Subject's Overall Assessment of Study Drug Efficacy for Each Episode of Severe Heartburn

Summary of subject's overall assessment of study drug efficacy for each severe heartburn episode is given below. This evaluation was performed at the end of each study-drug treated episode.

Summary of Subject Overall Episode Evaluation for Each Severe or Very Severe Episode During Treatment Phase
Protocol RAN3014
Intent-to-Treat Population

First Episode

	Ranitidine 75mg N=334	Ranitidine 150mg N=339	Placebo N=334
First Episode: Number of episodes	315	324	318
0=Not effective	24 (8%)	16 (5%)	38 (12%)
1=Poor	32 (10%)	35 (11%)	58 (10%)
2=Fair	62 (20%)	77 (24%)	66 (21%)
3=Good	101 (32%)	104 (32%)	80 (25%)
4=Very good	64 (20%)	63 (23%)	55 (17%)
5=Excellent	27 (9%)	26 (8%)	19 (6%)
Unknown	5 (2%)	3 (<1%)	2 (<1%)
Comparison with Placebo	<0.001	0.002	
Comparison with Ranitidine 75mg		0.925	

Copied from Table 19.
P-values were calculated using Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

All Episodes

	Ranitidine 75mg N=334	Ranitidine 150mg N=339	Placebo N=334
All Episode: Number of episodes	4814	4928	4633
0=Not effective	284 (6%)	270 (5%)	668 (14%)
1=Poor	571 (12%)	499 (10%)	672 (15%)
2=Fair	968 (20%)	1085 (22%)	923 (20%)
3=Good	1368 (28%)	1547 (31%)	1199 (26%)
4=Very good	1097 (23%)	1012 (21%)	749 (16%)
5=Excellent	456 (9%)	440 (9%)	369 (8%)
Unknown	70 (1%)	75 (2%)	53 (1%)
Comparison with Placebo	<0.001	<0.001	
Comparison with Ranitidine 75mg		0.942	

Copied from Table 19.
P-values were calculated using Generalized Estimating Equation with investigator in the model.

As seen from tables above, for treating the first study drug-treated heartburn episode, both ranitidine 150mg and ranitidine 75mg groups were more effective than placebo group. Comparison of the treatment groups revealed no significant difference between the ranitidine 150mg and the ranitidine 75mg groups.

For treating all of severe and very severe heartburn episodes, both ranitidine 150mg ranitidine 75mg groups were more effective than placebo group. No significant difference between the ranitidine groups was detected.

3.1.2.2.4.4 **Subject's Global Evaluation**

The result of analysis of subject's global evaluation at end of Treatment Phase is given below.

Summary of Subject's Global Evaluation at End of Treatment Phase
Protocol RAN3014
Intent-to-Treat Population

	Ranitidine 75mg N=334	Ranitidine 150mg N=339	Placebo N=334
Subjects with Global Evaluation	326	330	324
Subject's Global Evaluation			
0=Not effective	17(5%)	17 (5%)	35 (11%)
1=Poor	34 (10%)	25 (8%)	47 (15%)
2=Fair	69 (21%)	62 (19%)	62 (19%)
3=Good	93 (29%)	111 (34%)	97 (30%)
4=Very good	84 (26%)	90 (27%)	58 (18%)
5=Excellent	26 (8%)	22 (7%)	20 (6%)
Unknown	3 (<1%)	3 (<1%)	5 (2%)
Comparison with Placebo	0.005	<0.001	
Comparison with Ranitidine 75mg		0.252	

Copied from Table 20.
Correction was made in Adjustment to Clinical Report.
P-values were calculated using Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

As seen from table above, for the subject's global evaluation of the study drug as a treatment for severe heartburn, both ranitidine 150mg and ranitidine 75 groups were more effective than placebo group. Comparison of the treatment groups revealed no significant difference between the ranitidine 150mg and the ranitidine 75mg groups.

3.1.2.2.4.5 **Onset of Relief of Severe Heartburn Episodes**

The LOCFed pain relief scores were summarized by treatment group at 15 minutes, 30 minutes, 45 minutes, 1 hour, 1 hour 15 minutes, 1 hour 30 minutes, 1 hour 45 minutes, and 2 hours after study drug for severe heartburn episodes. For the First Episode, pairwise comparisons of the treatment groups at assessment timepoint were performed using a Wilcoxon rank sum test stratified by investigator (i.e., van Elteren test). For All Episodes, comparisons between the treatment groups were performed using Generalized Estimating Equation techniques.

Summaries of the LOCFed pain relief scores for the first study drug-treated episode at 15 minutes, 30 minutes, 45 minutes, 1 hour, 1 hour 15 minutes, 1 hour 30 minutes, 1 hour 45 minutes, and 2 hours after dosing in Appendix Tables 14 to 21, respectively.

As seen from Appendix Tables 14 to 21, at 15 minutes after study drug dosing, a slightly higher proportion of ranitidine 150mg subjects (4/324, 1%, p=0.044) experienced complete relief as compared to ranitidine 75mg (0/315, 0%). At one hour and 15 minutes after study drug dosing, the ranitidine 150mg group (302/324, 93%) had significantly greater proportions of subjects with little relief than did the ranitidine 75mg (277/315, 88%; p=0.020) or placebo groups (270/318, 85%; p<0.001). Additionally, at this same time there was differentiation between placebo and the ranitidine 150mg group for relief scores of "at least 2 (Some Relief)" (p=0.018).

3.1.2.2.4.6 **Duration of Relief of Severe Heartburn Episodes**

Duration of relief was computed as the number of hours between the first LOCFed pain relief score of at least "Little Relief" until the earliest time at which the subject re-dosed with study medication, used any antacid, or reported "No Relief." For the first severe episode analysis, treatment group comparisons were performed using an analysis of variance model with an investigator term.

The summary of duration (hours) of relief for both the first study drug-treated episode and across all study drug-treated episodes is given below.

Summary of Duration (Hours) of Relief
Protocol RAN3014
Intent-to-Treat Population

First Episode

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	314	14.0 (0.94)	9.4	0.062	
Ranitidine 150mg	321	13.7 (0.85)	9.8	0.093	0.847
Placebo	315	11.4 (1.02)	3.8		

Copied from Table 22.
P-values were calculated using analysis of variance stratified by investigator.

All Episodes

Treatment	N	Mean (SE)	Median	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	4489	11.1 (0.21)	6.8	0.039	
Ranitidine 150mg	4591	11.6 (0.21)	8.0	0.018	0.877
Placebo	4295	10.0 (0.22)	3.8		

Copied from Table 22.
P-values were calculated using Generalized Estimating Equation with investigator in the model.

As seen from tables above, for the first study drug-treated episode, mean duration of relief for both ranitidine 150mg and ranitidine 75mg groups were numerically longer than that of the placebo group. The duration of relief for the two ranitidine treatment groups was not significantly different.

For all study drug-treated episodes, both ranitidine 75mg and ranitidine 150mg failed to achieve statistical significance when compared to placebo at significance level of 0.0167 for adjusting for multiple comparisons. The ranitidine 150mg group and ranitidine 75mg group did not differ significantly.

3.1.2.2.4.7 **Rescue Antacid Use**

The definition of rescue antacid use was refined to consider antacid use identified on either the study drug treated or the non-study drug treated heartburn episode diary pages. Subjects who used any antacid within three hours of ingesting the study drug were

considered to have used rescue antacid. Number and proportion of subjects who used rescue antacid for a study drug-treated heartburn episode were summarized by treatment group. In the first severe episode analysis, treatment group comparisons were performed using a Cochran-Mantel-Haenszel test stratified by investigators.

Summary of rescue antacid use is given below.

Summary of Rescue Antacid Use
Protocol RAN3014
Intent-to-Treat Population

First Episode

Treatment	Used Antacid	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	85/315 (27%)	0.007	
Ranitidine 150mg	80/324 (25%)	0.001	0.543
Placebo	118/319 (37%)		

Copied from Table 23.
Correction was made in Adjustment to Clinical Report.
P-values were calculated using Mantel-Haenszel test stratified by investigator.

All Episodes

Treatment	Used Antacid	vs. Placebo p-value	vs. Ranitidine 75mg p-value
Ranitidine 75mg	1434/4814 (30%)	<0.001	
Ranitidine 150mg	1458/4928 (30%)	<0.001	0.792
Placebo	1739/4633 (38%)		

Copied from Table 23.
Correction was made in Adjustment to Clinical Report.
P-values were calculated using General Estimating Equations with investigator in the model.

As seen from table above, for the first study drug-treated heartburn episode, a statistically significantly smaller proportion of subjects in both ranitidine 75mg and ranitidine 150mg treatment groups utilized rescue antacid as compared to the placebo group. There was no significant difference between the two ranitidine groups in rescue antacid use.

For all drug-treated episodes, both ranitidine 75mg and ranitidine 150mg groups had a statistically significant smaller proportion of episodes rescued with antacid as compared to the placebo group. There was no significant difference between the two ranitidine groups.

3.1.2.2.4.8 Change in Abdominal-Gastric Index of Digestive Annoyance (AGIDA) Scores for Subjects Who Treated Severe Heartburn Episodes

Summary of Change in AGIDA scores for severe heartburn is given in Appendix Table 22.

As seen from Appendix Table 22, there was some improvement in the ranitidine 150mg groups' perceptions of "heartburn." There was some improvement in the ranitidine 75mg groups' perceptions of "heartburn," and "sour stomach."

3.1.2.2.4.9 **Peak Relief of Severe Heartburn Episode**

Number and proportion of subjects in each ordinal category of peak relief heartburn episodes were summarized by treatment group. Mean and median peak values were also summarized by treatment group and treatment group comparisons were performed using a Wilcoxon rank sum test stratified by investigator (i.e., van Elteren test).

Summary of the peak pain relief scores for the first study-treated heartburn episode is given below.

Summary of First Episode: Peak Relief Score of Severe or Very Severe Heartburn Episode
Protocol RAN3014
Intent-to-Treat Population

	Ranitidine 75mg N=334	Ranitidine 150mg N=339	Placebo N=334
First Episode Rated Severe or Very Severe	313	324	315
Peak Relief Score			
0=No Relief	17 (5%)	14 (4%)	31 (10%)
1=Little Relief	34 (11%)	26 (8%)	37 (12%)
2=Some Relief	30 (10%)	39 (12%)	41 (13%)
3=Moderate Relief	35 (11%)	45 (14%)	35 (11%)
4=Considerate Relief	53 (17%)	48 (15%)	46 (15%)
5=Almost Complete Relief	38 (12%)	49 (15%)	38 (12%)
6=Complete Relief	106 (34%)	103 (32%)	87 (28%)
Mean of peak relief scores	4.0	4.0	3.6
Median of peak relief scores	4.0	4.0	4.0
Comparison with Placebo	0.037	0.023	
Comparison with Ranitidine 75 mg		0.894	

Copied from Table 26.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

As seen from table above, for the first study drug-treated heartburn episode, both ranitidine 150mg and ranitidine 75mg groups did not achieved statistical significance when compared to placebo at significance level of 0.0167 for adjusting for multiple comparisons. The ranitidine 150mg did not differ from the ranitidine 75mg group.

3.1.2.2.4.10 **Severity of Other Heartburn Episodes over the Two Week Treatment Phase**

Summary of the number of non-study drug-treated heartburn episodes is given in Appendix Table 23.

As seen from Appendix Table 23, in general, the mean number of non-study drug – treated episodes were similar across treatment groups.

3.1.2.2.4.11 Relief of Nighttime Heartburn Affect Sleep over the Two Week Treatment Phase

Summary of relief of nighttime heartburn affecting sleep during Treatment Phase is given in Appendix Table 24.

As seen from Appendix Table 24, there were no treatment group differences in the relief of nighttime heartburn affecting sleep during Treatment Phase.

3.1.2.3 Reviewer's Comments and Evaluation

3.1.2.3.1 Multiplicity Issue

In the protocol, it stated that the primary statistical comparison was the pairwise comparison of the ranitidine 150mg and ranitidine 75mg. As there was only one primary comparison on one primary endpoint, no multiple comparisons adjustment to p-value was planned.

But, this study showed that there was no statistical significant difference between ranitidine 150mg and ranitidine 75mg in terms of total pain relief (TOTPAR) (p=0.980). For further testing between ranitidine 150mg and placebo and between ranitidine 75mg and placebo, the p-values should be adjusted for multiplicity. To be conservative, the Bonferroni method should be applied. Each of the active treatments was compared to placebo at the an $\alpha/3$ (0.0167) level of significance.

3.1.2.3.2 LOCF Analyses

The comments stated fro Protocol RAN3013 also apply to this study.

3.1.2.3.3 Reviewer's Comments on Sponsor's Analysis of Primary Efficacy Endpoint

3.1.2.3.4.1 TOTPAR Scores for First Episode

For the pre-specified primary endpoint, total pain relief score (TOTPAR) of severe or very severe heartburn over 2-hour evaluation period for first episode, it was shown that after adjusting for multiple comparisons, there was not statistically significant difference in TOTPAR score between the ranitidine 150mg and placebo groups for both Intent-to-Treat and efficacy evaluable populations. There was not statistically significant difference in TOTPAR score between the ranitidine 75mg and placebo groups for both Intent-to-Treat and efficacy evaluable populations. The treatment difference of medians between ranitidine 150mg and placebo was 2.0 for Intent-to-Treat population.

There was no statistically significant difference between the ranitidine 150mg and ranitidine 75 groups. The treatment difference of medians between ranitidine 150mg and ranitidine 75mg was 1.0 for Intent-to-Treat population.

3.1.2.3.4.2 **Subgroup Analysis**

The sponsor also performed subgroup analyses of the primary efficacy endpoint by race (white vs. non white), gender, and age (<65 vs. ≥65). The results for subgroup analyses are given below.

Total Pain Relief (TOTPAR) Scores for First Episode by Subgroup

Protocol RAN3014
Intent-to-Treat Population

Subgroup	Ranitidine 75mg N	Mean	Median	Ranitidine 150mg N	Mean	Median	Placebo N	Mean	Median	Ran 75mg vs Placebo P-value	Ran 150mg vs. Placebo P-value	Ran 75mg vs. Ran 150mg P-value
Race												
White	258	21.0	21.0	270	21.1	20.0	262	19.0	18.0	0.052	0.064	0.936
Non-White	55	19.4	19.0	54	21.1	21.5	53	19.5	18.0	0.729	0.604	0.372
Gender												
Male	169	20.1	20.0	171	21.1	20.0	172	19.6	19.0	0.550	0.256	0.868
Female	144	21.4	21.5	153	21.0	20.0	143	18.5	18.0	0.226	0.236	0.899
Age												
<65	296	20.4	20.5	312	21.2	20.0	298	18.8	18.0	0.114	0.019	0.693
≥65	17	25.9	30.0	12	18.1	17.0	17	24.6	25.0	0.769	0.242	0.403
Tobacco User												
Yes	91	20.8	22.0	111	21.2	20.0	88	19.2	18.5	0.148	0.139	0.893
No	222	20.7	20.0	213	21.0	20.0	227	19.1	18.0	0.222	0.094	0.888
Maximum two doses												
Yes	21	17.5	23.0	30	15.4	11.0	22	14.2	11.5	0.434	0.369	0.770
No	292	20.9	21.0	294	21.7	20.5	293	19.5	19.0	0.117	0.029	0.772

Copied from Tables 17.02-17.11.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

As seen from table above, subjects with maximum less than two doses had higher TOTAP score for first episode than subjects with maximum two doses. Superiority of ranitidine 150mg versus placebo was not consistent across subgroups of race, gender, tobacco user, and subjects with maximum two doses.

3.1.2.3.4.3 **Reviewer's Comments on Sponsor's Analysis of Secondary Efficacy Endpoints**

For total pain relief score (TOTPAR) of severe or very severe heartburn over 2-hour evaluation period for all study drug -treated episodes, it was shown that there were statistically significant differences in TOTPAR scores between the ranitidine 150mg and placebo for the Intent-to-Treat population. For efficacy evaluable population, it just failed to achieve statistical significance level of 0.0167. The ranitidine 75mg was not

statistically significantly different from placebo. No statistically significant difference was observed between ranitidine groups.

This study revealed that the ranitidine 150mg group was more effective than placebo in 3 of 8 secondary efficacy endpoints: subject's overall assessment of study drug efficacy for each episode of severe heartburn, subject's global evaluation, and rescue antacid use.

The ranitidine 75mg group was more effective than placebo in 4 of 8 secondary efficacy endpoints: subject's overall assessment of study drug efficacy for each episode of severe heartburn, subject's global evaluation, rescue antacid use and change in AGIDA scores for subjects who treated severe heartburn episodes.

3.2 Evaluation of Safety

In Study RAN3013, during the Treatment Phase, the proportion of subjects' experiencing any adverse event was statistically different across treatment groups. Twelve percent (12%, 39/338) of ranitidine 150mg subjects, 12% (39/338) of ranitidine 75mg subjects, and 18% (51/337) of placebo subjects reported adverse events (p=0.020). Within body systems, a statistically significant difference existed for the ear/nose/throat (p=0.012) and the gastrointestinal (p=0.048) categories; with the incidence of adverse events highest in the placebo group.

In Study RAN3014, during the Treatment Phase, the proportion of subjects' experiencing any adverse event was not statistically different across treatment groups.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The results for subgroup analyses of the primary efficacy endpoint by race, gender, and age for studies RAN3013 and RAN3014 are given below.

Total Pain Relief (TOTPAR) Scores for First Episode by Subgroup

Protocol RAN3013
Intent-to-Treat Population

Subgroup	Ranitidine 75mg N	Mean	Median	Ranitidine 150mg N	Mean	Median	Placebo N	Mean	Median	Ran 75mg vs Placebo P-value	Ran 150mg vs. Placebo P-value	Ran 75mg vs. Ran 150mg P-value
Race												
White	259	20.0	20.0	262	20.3	19.5	262	17.5	16.0	0.048	0.019	0.640
Non-White	64	20.5	19.0	51	21.8	21.0	58	17.5	15.5	0.857	0.208	0.933
Gender												
Male	167	21.7	21.0	167	21.4	21.0	155	18.0	16.0	0.077	0.030	0.887
Female	156	18.5	18.0	146	19.7	19.0	165	17.0	15.0	0.568	0.188	0.584
Age												
<65	315	20.1	19.0	298	20.2	20.0	303	17.5	16.0	0.016	0.010	0.827
≥65	8	21.0	19.5	15	28.0	30.0	17	17.7	20.0	0.330	0.943	0.321

Copied from Tables 17.02-17.11.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

Protocol RAN3014
Intent-to-Treat Population

Subgroup	Ranitidine 75mg N	Mean	Median	Ranitidine 150mg N	Mean	Median	Placebo N	Mean	Median	Ran 75mg vs Placebo P-value	Ran 150mg vs. Placebo P-value	Ran 75mg vs. Ran 150mg P-value
Race												
White	258	21.0	21.0	270	21.1	20.0	262	19.0	18.0	0.052	0.064	0.936
Non-White	55	19.4	19.0	54	21.1	21.5	53	19.5	18.0	0.729	0.604	0.372
Gender												
Male	169	20.1	20.0	171	21.1	20.0	172	19.6	19.0	0.550	0.256	0.868
Female	144	21.4	21.5	153	21.0	20.0	143	18.5	18.0	0.226	0.236	0.899
Age												
<65	296	20.4	20.5	312	21.2	20.0	298	18.8	18.0	0.114	0.019	0.693
≥65	17	25.9	30.0	12	18.1	17.0	17	24.6	25.0	0.769	0.242	0.403

Copied from Tables 17.02-17.11.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

As seen from tables above, superiority of ranitidine 150mg versus placebo was not consistent across subgroups of race, gender, and age.

4.2 Other Special/Subgroup Populations

The results for subgroup analyses of the primary efficacy endpoint by tobacco use and maximum two doses for studies RAN3013 and RAN3014 are given below.

Total Pain Relief (TOTPAR) Scores for First Episode by Subgroup
Protocol RAN3013
Intent-to-Treat Population

Subgroup	Ranitidine 75mg N	Mean	Median	Ranitidine 150mg N	Mean	Median	Placebo N	Mean	Median	Ran 75mg vs Placebo P-value	Ran 150mg vs. Placebo P-value	Ran 75mg vs. Ran 150mg P-value
Tobacco User												
Yes	102	18.5	19.0	108	19.6	19.0	96	16.1	13.0	0.241	0.065	0.720
No	221	20.9	19.0	205	21.0	21.0	224	18.1	17.0	0.083	0.012	0.770
Maximum two doses												
Yes	31	14.4	14.0	26	17.0	17.0	19	11.9	10.0	0.245	0.484	0.330
No	292	20.7	20.0	287	20.9	21.0	301	17.9	16.0	0.014	0.006	0.615

Copied from Tables 17.02-17.11.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

Protocol RAN3014
Intent-to-Treat Population

Subgroup	Ranitidine 75mg N	Mean	Median	Ranitidine 150mg N	Mean	Median	Placebo N	Mean	Median	Ran 75mg vs Placebo P-value	Ran 150mg vs. Placebo P-value	Ran 75mg vs. Ran 150mg P-value
Tobacco User												
Yes	91	20.8	22.0	111	21.2	20.0	88	19.2	18.5	0.148	0.139	0.893
No	222	20.7	20.0	213	21.0	20.0	227	19.1	18.0	0.222	0.094	0.888
Maximum two doses												
Yes	21	17.5	23.0	30	15.4	11.0	22	14.2	11.5	0.434	0.369	0.770
No	292	20.9	21.0	294	21.7	20.5	293	19.5	19.0	0.117	0.029	0.772

Copied from Tables 17.02-17.11.
P-values were calculated using a Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).

As seen from tables above, subjects with maximum less than two doses had higher TOTPAR score for first episode than subjects with maximum two doses.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

In the protocol, it stated that the primary statistical comparison was the pairwise comparison of the ranitidine 150mg and ranitidine 75mg. As there was only one primary comparison on one primary endpoint, no multiple comparisons adjustment to p-value was planned.

But, Both studies (RAN3013 and RAN3014) showed that there was no statistical significant difference between ranitidine 150mg and ranitidine 75mg in terms of total pain relief (TOTPAR) (p=0.567 in RAN3013 and p=0.980 in RAN3014). For further testing between ranitidine 150mg and placebo and between ranitidine 75mg and placebo,

the p-values should be adjusted for multiplicity. To be conservative, the Bonferroni method should be applied. Each of the active treatments was compared to placebo at the an $\alpha/3$ (0.0167) level of significance.

For the pre-specified primary endpoint, total pain relief score (TOTPAR) of severe or very severe heartburn over 2-hour evaluation period for first episode, study RAN3013 showed that there was a statistically significant difference in TOTPAR score between the ranitidine 150mg and placebo for both Intent-to-Treat and efficacy evaluable populations. There was a statistically significant difference in TOTPAR score between the ranitidine 75mg and placebo for the Intent-to-Treat population. For efficacy evaluable population, the treatment difference between ranitidine 75mg and placebo just failed to reach statistical significance level of 0.0167 adjusting for multiple comparisons. The treatment difference of medians between ranitidine 150mg and placebo was 5.0 for both Intent-to-Treat and efficacy evaluable populations.

Study RAN3014 showed that after adjusting for multiple comparisons, there was not statistically significant difference in TOTPAR score between the ranitidine 150mg and placebo groups for both Intent-to-Treat and efficacy evaluable populations. There was not statistically significant difference in TOTPAR score between the ranitidine 75mg and placebo groups for both Intent-to-Treat and efficacy evaluable populations. The treatment difference of medians between ranitidine 150mg and placebo was 2.0 for Intent-to-Treat population.

Both studies (RAN3013 and RAN3014) showed that there was no statistically significant difference between the ranitidine 150mg and ranitidine 75 groups. The treatment differences of medians between ranitidine 150mg and ranitidine 75mg were 2.0 and 1.0, respectively for studies RAN3013 and RAN3014 for Intent-to-Treat population.

For the secondary efficacy endpoints, for total pain relief score (TOTPAR) of severe or very severe heartburn over 2-hour evaluation period for all study drug -treated episodes, study RAN3013 showed that there were statistically significant differences in TOTPAR scores between the ranitidine 150mg and placebo and between ranitidine 75mg and placebo for both Intent-to-Treat and efficacy evaluable populations.

Study RAN3013 revealed that both ranitidine 75mg and ranitidine 150mg groups were more effective than placebo in 3 of 8 secondary efficacy endpoints: subject's overall assessment of study drug efficacy for each episode of severe heartburn, subject's global evaluation, and peak relief of severe heartburn episodes.

For total pain relief score (TOTPAR) of severe or very severe heartburn over 2-hour evaluation period for all study drug -treated episodes, study RAN3014 showed that there were statistically significant differences in TOTPAR scores between the ranitidine 150mg and placebo for the Intent-to-Treat population. For efficacy evaluable population, it just failed to achieve statistical significance level of 0.0167. The ranitidine 75mg was not statistically significantly different from placebo. No statistically significant difference was observed between ranitidine groups.

Study RAN3014 revealed that the ranitidine 150mg group was more effective than placebo in 3 of 8 secondary efficacy endpoints: subject's overall assessment of study drug efficacy for each episode of severe heartburn, subject's global evaluation, and rescue antacid use.

The ranitidine 75mg group was more effective than placebo in 4 of 8 secondary efficacy endpoints: subject's overall assessment of study drug efficacy for each episode of severe heartburn, subject's global evaluation, rescue antacid use and change in AGIDA scores for subjects who treated severe heartburn episodes.

5.2 Conclusion and Recommendations

In Study RAN3013, for the pre-specified primary endpoint, total pain relief score (TOTPAR) of severe or very severe heartburn over 2-hour evaluation period for first episode, it was shown that there was a statistically significant difference in TOTPAR score between the ranitidine 150mg and placebo for both Intent-to-Treat and efficacy evaluable populations. There was a statistically significant difference in TOTPAR score between the ranitidine 75mg and placebo for the Intent-to-Treat population. For efficacy evaluable population, the treatment difference between ranitidine 75mg and placebo just failed to reach statistical significance level of 0.0167 adjusting for multiple comparisons. There was no statistically significant difference between the ranitidine 150mg and ranitidine 75 groups.

For total pain relief score (TOTPAR) of severe or very severe heartburn over 2-hour evaluation period for all study drug -treated episodes, it was shown that there were statistically significant differences in TOTPAR scores between the ranitidine 150mg and placebo and between ranitidine 75mg and placebo for both Intent-to-Treat and efficacy evaluable populations. There was no statistically significant difference between ranitidine 75mg and ranitidine 150mg.

This study revealed that both ranitidine 75mg and ranitidine 150mg groups were more effective than placebo in 3 of 8 secondary efficacy endpoints: subject's overall assessment of study drug efficacy for each episode of severe heartburn, subject's global evaluation, and peak relief of severe heartburn episodes.

In Study RAN3014, for the pre-specified primary endpoint, total pain relief score (TOTPAR) of severe or very severe heartburn over 2-hour evaluation period for first episode, it was shown that after adjusting for multiple comparisons, there was not statistically significant difference in TOTPAR score between the ranitidine 150mg and placebo groups for both Intent-to-Treat and efficacy evaluable populations. There was not statistically significant difference in TOTPAR score between the ranitidine 75mg and placebo groups for both Intent-to-Treat and efficacy evaluable populations. There was no statistically significant difference between the ranitidine 150mg and ranitidine 75 groups.

For total pain relief score (TOTPAR) of severe or very severe heartburn over 2-hour evaluation period for all study drug -treated episodes, it was shown that there were statistically significant differences in TOTPAR scores between the ranitidine 150mg and placebo for the Intent-to-Treat population. For efficacy evaluable population, it failed to achieve statistical significance level of 0.0167 adjusting for multiple comparisons.. The ranitidine 75mg was not statistically significantly different from placebo. No statistically significant difference was observed between ranitidine groups.

This study revealed that the ranitidine 150mg group was more effective than placebo in 3 of 8 secondary efficacy endpoints: subject's overall assessment of study drug efficacy for each episode of severe heartburn, subject's global evaluation, and rescue antacid use.

The ranitidine 75mg group was more effective than placebo in 4 of 8 secondary efficacy endpoints: subject's overall assessment of study drug efficacy for each episode of severe heartburn, subject's global evaluation, rescue antacid use and change in AGIDA scores for subjects who treated severe heartburn episodes.

In conclusion, only Study RANA3013 demonstrated that both ranitidine 75mg and ranitidine 150mg were statistically significantly better than placebo for first study drug treated episode for analysis of total pain relief (TOTPAR). Study 3014 showed dose related trends, though the differences between ranitidine 150mg and ranitidine 75mg were not statistically significant.

6. APPENDIX

Table 1 Baseline Patient Characteristic by Treatment Group --- Protocol RANA3013
All Randomized

Characteristic	Ranitidine 75 mg (N=338)	Ranitidine 150 mg (N=338)	Placebo (N=337)	Among Groups p-value
Gender				0.596
Male	171 (51%)	181 (54%)	168 (50%)	
Female	167 (49%)	157 (46%)	169 (50%)	
Race				0.740
Caucasian	271 (80%)	285 (84%)	276 (82%)	
Black	52 (15%)	40 (12%)	44 (13%)	
Hispanic	13 (4%)	9 (3%)	14 (4%)	
Oriental	0	2 (<1%)	1 (<1%)	
Other	2 (<1%)	2 (<1%)	2 (<1%)	
Age (yr)				0.060
Mean (SD)	40.8 (11.0)	40.9 (12.0)	42.8 (12.1)	
Height (inches)				0.664
Mean (SD)	67.6 (4.0)	67.6 (4.0)	67.3 (4.2)	
Weight (lbs)				0.782
N	338	337	337	
Mean (SD)	194.7 (42.3)	193.4 (39.8)	196.4 (43.5)	
Tobacco Use				0.560
No	232 (69%)	221 (65%)	232 (69%)	
Yes	106 (31%)	117 (35%)	105 (31%)	
Length of time (yrs) with heartburn, acid indigestion or sour stomach				0.265
Mean (SD)	10.1 (9.2)	9.5 (9.2)	11.0 (11.0)	
Did you ever see a doctor because of your heartburn, sour stomach or acid indigestion				0.866
No	185 (55%)	184 (54%)	178 (53%)	
Yes	153 (45%)	154 (46%)	159 (47%)	
How many days did you experience heartburn over the last week?				0.170
Mean (SD)	6.1 (1.1)	6.2 (1.1)	6.1 (1.1)	

Copied from Tables 7, 10 and 11.
P-value was calculated using Kruskal-Wallis test for continuous data.
P-value was calculated using Cochran-Mantel-Haenszel test for categorical data.

Table 1 Baseline Patient Characteristic by Treatment Group --- Protocol RANA3013
(Continued)

All Randomized

Characteristic	Ranitidine 75 mg (N=338)	Ranitidine 150 mg (N=338)	Placebo (N=337)	Among Groups p-value
How many days did you experience heartburn over the week before?				0.290
Mean (SD)	6.1 (1.1)	6.2 (1.1)	6.1 (1.1)	
On a typical day how many episodes of heartburn do you have?				0.175
Mean (SD)	2.7 (1.7)	2.7 (1.8)	2.6 (1.7)	
Describe most of your heartburn episodes over the last two weeks				0.326
Very mild	0	0	0	
Mild	0	0	0	
Moderate	0	0	0	
Severe	268 (79%)	280 (83%)	281 (83%)	
Very severe	70 (21%)	58 (17%)	56 (17%)	
What do you usually take for heartburn?				
Antacids	268 (79%)	277 (82%)	259 (77%)	0.262
OTC H2's	147 (43%)	151 (45%)	154 (46%)	0.847
Prescription H2's	35 (10%)	28 (8%)	36 (11%)	0.523
Pepto Bismol	14 (4%)	10 (3%)	12 (4%)	0.708
Other	28 (8%)	23 (7%)	27 (8%)	0.745
Frequency of heartburn medication				0.723
not every day	76 (22%)	69 (20%)	74 (22%)	
Daily – once per day	53 (16%)	66 (20%)	64 (19%)	
Daily – more than once per day	205 (61%)	199 (59%)	199 (59%)	

Copied from Tables 11and 12.
P-value was calculated using Kruskal-Wallis test for continuous data.
P-value was calculated using Cochran-Mantel-Haenszel test for categorical data.

Table 2 Summary of First Heartburn Episode Pain Relief Scores at 15 Minutes --- RAN3013

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Table 18
Summary of First Heartburn Episode Pain Relief Scores at 15 Minutes

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	337	338	338
First Episode Rated Severe or Very Severe	320	323	315
Relief Score of at least 1 (Little Relief)			
Yes	100 (31%)	104 (32%)	104 (33%)
No	220 (69%)	219 (68%)	211 (67%)
Comparison with Ranitidine 75mg [1]			0.825
Comparison with Placebo [1]		0.878	0.633
Relief Score of at least 2 (Some Relief)			
Yes	44 (14%)	47 (15%)	44 (14%)
No	276 (86%)	276 (85%)	271 (86%)
Comparison with Ranitidine 75mg [1]			0.875
Comparison with Placebo [1]		0.864	0.914
Relief Score of at least 3 (Moderate Relief)			
Yes	20 (6%)	27 (8%)	26 (8%)
No	300 (94%)	296 (92%)	289 (92%)
Comparison with Ranitidine 75mg [1]			0.987
Comparison with Placebo [1]		0.330	0.302

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

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Table 18 (Continued)
Summary of First Heartburn Episode Pain Relief Scores at 15 Minutes

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	337	338	338
First Episode Rated Severe or Very Severe	320	323	315
Relief score of at least 4 (Considerate Relief)			
Yes	8 (3%)	13 (4%)	15 (5%)
No	312 (98%)	310 (96%)	300 (95%)
Comparison with Ranitidine 75mg [1]			0.651
Comparison with Placebo [1]		0.301	0.115
Relief Score of at least 5 (Almost Complete Relief)			
Yes	3 (<1%)	4 (1%)	8 (3%)
No	317(>99%)	319 (99%)	307 (97%)
Comparison with Ranitidine 75mg [1]			0.231
Comparison with Placebo [1]		0.746	0.123
Relief Score of at least 6 (Complete Relief)			
Yes	2 (<1%)	3 (<1%)	5 (2%)
No	318(>99%)	320(>99%)	310 (98%)
Comparison with Ranitidine 75mg [1]			0.454
Comparison with Placebo [1]		0.701	0.241

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

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Table 3 Summary of First Heartburn Episode Pain Relief Scores at 30 Minutes --- RAN3013

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ON ORIGINAL

Table 18.1
Summary of First Heartburn Episode Pain Relief Scores at 30 Minutes

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	337	338	338
First Episode Rated Severe or Very Severe	320	323	315
Relief Score of at least 1 (Little Relief)			
Yes	173 (54%)	176 (54%)	182 (58%)
No	147 (46%)	147 (46%)	133 (42%)
Comparison with Ranitidine 75mg [1]			0.373
Comparison with Placebo [1]		0.951	0.328
Relief Score of at least 2 (Some Relief)			
Yes	91 (28%)	105 (33%)	92 (29%)
No	229 (72%)	218 (67%)	223 (71%)
Comparison with Ranitidine 75mg [1]			0.399
Comparison with Placebo [1]		0.297	0.788
Relief Score of at least 3 (Moderate Relief)			
Yes	48 (15%)	58 (18%)	50 (16%)
No	272 (85%)	265 (82%)	265 (84%)
Comparison with Ranitidine 75mg [1]			0.526
Comparison with Placebo [1]		0.369	0.753

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

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Table 18.1 (Continued)
Summary of First Heartburn Episode Pain Relief Scores at 30 Minutes

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	337	338	338
First Episode Rated Severe or Very Severe	320	323	315
Relief score of at least 4 (Considerate Relief)			
Yes	22 (7%)	34 (11%)	32 (10%)
No	298 (93%)	289 (89%)	283 (90%)
Comparison with Ranitidine 75mg [1]			0.889
Comparison with Placebo [1]		0.116	0.124
Relief Score of at least 5 (Almost Complete Relief)			
Yes	10 (3%)	18 (6%)	18 (6%)
No	310 (97%)	305 (94%)	297 (94%)
Comparison with Ranitidine 75mg [1]			0.952
Comparison with Placebo [1]		0.152	0.117
Relief Score of at least 6 (Complete Relief)			
Yes	3 (<1%)	10 (3%)	13 (4%)
No	317(>99%)	313 (97%)	302 (96%)
Comparison with Ranitidine 75mg [1]			0.492
Comparison with Placebo [1]		0.061	0.011

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

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Table 4 Summary of First Heartburn Episode Pain Relief Scores at 45 Minutes --- RAN3013

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Table 18.2
Summary of First Heartburn Episode Pain Relief Scores at 45 Minutes

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	337	338	338
First Episode Rated Severe or Very Severe	320	323	315
Relief Score of at least 1 (Little Relief)			
Yes	228 (71%)	256 (79%)	243 (77%)
No	92 (29%)	67 (21%)	72 (23%)
Comparison with Ranitidine 75mg [1]			0.579
Comparison with Placebo [1]		0.023	0.080
Relief Score of at least 2 (Some Relief)			
Yes	144 (45%)	153 (47%)	156 (50%)
No	176 (55%)	170 (53%)	159 (50%)
Comparison with Ranitidine 75mg [1]			0.500
Comparison with Placebo [1]		0.619	0.225
Relief Score of at least 3 (Moderate Relief)			
Yes	86 (27%)	101 (31%)	96 (30%)
No	234 (73%)	222 (69%)	219 (70%)
Comparison with Ranitidine 75mg [1]			0.871
Comparison with Placebo [1]		0.249	0.297

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

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Table 18.2 (Continued)
Summary of First Heartburn Episode Pain Relief Scores at 45 Minutes

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	337	338	338
First Episode Rated Severe or Very Severe	320	323	315
Relief score of at least 4 (Considerate Relief)			
Yes	44 (14%)	60 (19%)	62 (20%)
No	276 (86%)	263 (81%)	253 (80%)
Comparison with Ranitidine 75mg [1]			0.647
Comparison with Placebo [1]		0.115	0.043
Relief Score of at least 5 (Almost Complete Relief)			
Yes	27 (8%)	34 (11%)	40 (13%)
No	293 (92%)	289 (89%)	275 (87%)
Comparison with Ranitidine 75mg [1]			0.363
Comparison with Placebo [1]		0.414	0.074
Relief Score of at least 6 (Complete Relief)			
Yes	10 (3%)	19 (6%)	22 (7%)
No	310 (97%)	304 (94%)	293 (93%)
Comparison with Ranitidine 75mg [1]			0.540
Comparison with Placebo [1]		0.116	0.026

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

Table 5 Summary of First Heartburn Episode Pain Relief Scores at 1 Hour --- RAN3013

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Table 18.3
Summary of First Heartburn Episode Pain Relief Scores at 1 Hour

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	337	338	338
First Episode Rated Severe or Very Severe	320	323	315
Relief Score of at least 1 (Little Relief)			
Yes	248 (78%)	271 (84%)	271 (86%)
No	72 (23%)	52 (16%)	44 (14%)
Comparison with Ranitidine 75mg [1]			0.416
Comparison with Placebo [1]		0.040	0.005
Relief Score of at least 2 (Some Relief)			
Yes	183 (57%)	222 (69%)	201 (64%)
No	137 (43%)	101 (31%)	114 (36%)
Comparison with Ranitidine 75mg [1]			0.216
Comparison with Placebo [1]		0.003	0.086
Relief Score of at least 3 (Moderate Relief)			
Yes	117 (37%)	142 (44%)	143 (45%)
No	203 (63%)	181 (56%)	172 (55%)
Comparison with Ranitidine 75mg [1]			0.654
Comparison with Placebo [1]		0.062	0.020

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

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Table 18.3 (Continued)
Summary of First Heartburn Episode Pain Relief Scores at 1 Hour

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	337	338	338
First Episode Rated Severe or Very Severe	320	323	315
Relief score of at least 4 (Considerate Relief)			
Yes	71 (22%)	99 (31%)	99 (31%)
No	249 (78%)	224 (69%)	216 (69%)
Comparison with Ranitidine 75mg [1]			0.785
Comparison with Placebo [1]		0.019	0.008
Relief Score of at least 5 (Almost Complete Relief)			
Yes	47 (15%)	67 (21%)	66 (21%)
No	273 (85%)	256 (79%)	249 (79%)
Comparison with Ranitidine 75mg [1]			0.876
Comparison with Placebo [1]		0.060	0.032
Relief Score of at least 6 (Complete Relief)			
Yes	25 (8%)	46 (14%)	41 (13%)
No	295 (92%)	277 (86%)	274 (87%)
Comparison with Ranitidine 75mg [1]			0.697
Comparison with Placebo [1]		0.012	0.029

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

Table 6 Summary of First Heartburn Episode Pain Relief Scores at 1 Hour 15 Minutes --- RAN3013

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Table 18.4
Summary of First Heartburn Episode Pain Relief Scores at 1 Hour 15 Minutes

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	337	338	338
First Episode Rated Severe or Very Severe	320	323	315
Relief Score of at least 1 (Little Relief)			
Yes	269 (84%)	281 (87%)	280 (89%)
No	51 (16%)	42 (13%)	35 (11%)
Comparison with Ranitidine 75mg [1]			0.414
Comparison with Placebo [1]		0.318	0.078
Relief Score of at least 2 (Some Relief)			
Yes	206 (64%)	236 (73%)	227 (72%)
No	114 (36%)	87 (27%)	88 (28%)
Comparison with Ranitidine 75mg [1]			0.832
Comparison with Placebo [1]		0.022	0.037
Relief Score of at least 3 (Moderate Relief)			
Yes	149 (47%)	184 (57%)	175 (56%)
No	171 (53%)	139 (43%)	140 (44%)
Comparison with Ranitidine 75mg [1]			0.783
Comparison with Placebo [1]		0.010	0.022

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

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Table 18.4 (Continued)
Summary of First Heartburn Episode Pain Relief Scores at 1 Hour 15 Minutes

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	337	338	338
First Episode Rated Severe or Very Severe	320	323	315
Relief score of at least 4 (Considerate Relief)			
Yes	100 (31%)	130 (40%)	128 (41%)
No	220 (69%)	193 (60%)	187 (59%)
Comparison with Ranitidine 75mg [1]			0.859
Comparison with Placebo [1]		0.019	0.012
Relief Score of at least 5 (Almost Complete Relief)			
Yes	61 (19%)	92 (28%)	86 (27%)
No	259 (81%)	231 (72%)	229 (73%)
Comparison with Ranitidine 75mg [1]			0.823
Comparison with Placebo [1]		0.008	0.013
Relief Score of at least 6 (Complete Relief)			
Yes	38 (12%)	65 (20%)	59 (19%)
No	282 (88%)	258 (80%)	256 (81%)
Comparison with Ranitidine 75mg [1]			0.707
Comparison with Placebo [1]		0.006	0.015

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

Table 7 Summary of First Heartburn Episode Pain Relief Scores at 1 Hour 30 Minutes --- RAN3013

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Table 18.5
Summary of First Heartburn Episode Pain Relief Scores at 1 Hour 30 Minutes

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	337	338	338
First Episode Rated Severe or Very Severe	320	323	315
Relief Score of at least 1 (Little Relief)			
Yes	278 (87%)	285 (88%)	289 (92%)
No	42 (13%)	38 (12%)	26 (8%)
Comparison with Ranitidine 75mg [1]			0.109
Comparison with Placebo [1]		0.652	0.050
Relief Score of at least 2 (Some Relief)			
Yes	218 (68%)	247 (76%)	246 (78%)
No	102 (32%)	76 (24%)	69 (22%)
Comparison with Ranitidine 75mg [1]			0.586
Comparison with Placebo [1]		0.022	0.004
Relief Score of at least 3 (Moderate Relief)			
Yes	173 (54%)	203 (63%)	195 (62%)
No	147 (46%)	120 (37%)	120 (38%)
Comparison with Ranitidine 75mg [1]			0.827
Comparison with Placebo [1]		0.026	0.040

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

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Table 18.5 (Continued)
Summary of First Heartburn Episode Pain Relief Scores at 1 Hour 30 Minutes

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	337	338	338
First Episode Rated Severe or Very Severe	320	323	315
Relief score of at least 4 (Considerate Relief)			
Yes	121 (38%)	149 (46%)	160 (51%)
No	199 (62%)	174 (54%)	155 (49%)
Comparison with Ranitidine 75mg [1]			0.226
Comparison with Placebo [1]		0.033	<0.001
Relief Score of at least 5 (Almost Complete Relief)			
Yes	79 (25%)	110 (34%)	104 (33%)
No	241 (75%)	213 (66%)	211 (67%)
Comparison with Ranitidine 75mg [1]			0.853
Comparison with Placebo [1]		0.012	0.018
Relief Score of at least 6 (Complete Relief)			
Yes	52 (16%)	76 (24%)	76 (24%)
No	268 (84%)	247 (76%)	239 (76%)
Comparison with Ranitidine 75mg [1]			0.812
Comparison with Placebo [1]		0.030	0.013

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

Table 8 Summary of First Heartburn Episode Pain Relief Scores at 1 Hour 45 Minutes --- RAN3013

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Table 10.6
Summary of First Heartburn Episode Pain Relief Scores at 1 Hour 45 Minutes

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	337	338	338
First Episode Rated Severe or Very Severe	320	323	315
Relief Score of at least 1 (Little Relief)			
Yes	283 (88%)	283 (88%)	291 (92%)
No	37 (12%)	40 (12%)	24 (8%)
Comparison with Ranitidine 75mg [1]			0.037
Comparison with Placebo [1]		0.672	0.094
Relief Score of at least 2 (Some Relief)			
Yes	231 (72%)	259 (80%)	254 (81%)
No	89 (28%)	64 (20%)	61 (19%)
Comparison with Ranitidine 75mg [1]			0.831
Comparison with Placebo [1]		0.020	0.010
Relief Score of at least 3 (Moderate Relief)			
Yes	190 (59%)	218 (67%)	213 (68%)
No	130 (41%)	105 (33%)	102 (32%)
Comparison with Ranitidine 75mg [1]			0.943
Comparison with Placebo [1]		0.037	0.026

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

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Table 18.6 (Continued)
Summary of First Heartburn Episode Pain Relief Scores at 1 Hour 45 Minutes

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	337	338	338
First Episode Rated Severe or Very Severe	320	323	315
Relief score of at least 4 (Considerate Relief)			
Yes	146 (46%)	165 (51%)	177 (56%)
No	174 (54%)	158 (49%)	138 (44%)
Comparison with Ranitidine 75mg [1]			0.177
Comparison with Placebo [1]		0.186	0.007
Relief Score of at least 5 (Almost Complete Relief)			
Yes	101 (32%)	139 (43%)	132 (42%)
No	219 (68%)	184 (57%)	183 (58%)
Comparison with Ranitidine 75mg [1]			0.816
Comparison with Placebo [1]		0.003	0.006
Relief Score of at least 6 (Complete Relief)			
Yes	69 (22%)	90 (28%)	94 (30%)
No	251 (78%)	233 (72%)	221 (70%)
Comparison with Ranitidine 75mg [1]			0.561
Comparison with Placebo [1]		0.077	0.015

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

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Table 9 Summary of First Heartburn Episode Pain Relief Scores at 2 Hours ---RAN3013

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ON ORIGINAL

Table 18.7
Summary of First Heartburn Episode Pain Relief Scores at 2 Hours

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	337	338	338
First Episode Rated Severe or Very Severe	320	323	315
Relief Score of at least 1 (Little Relief)			
Yes	283 (88%)	285 (88%)	292 (93%)
No	37 (12%)	38 (12%)	23 (7%)
Comparison with Ranitidine 75mg [1]			0.043
Comparison with Placebo [1]		0.846	0.066
Relief Score of at least 2 (Some Relief)			
Yes	242 (76%)	258 (80%)	256 (81%)
No	78 (24%)	65 (20%)	59 (19%)
Comparison with Ranitidine 75mg [1]			0.590
Comparison with Placebo [1]		0.247	0.075
Relief Score of at least 3 (Moderate Relief)			
Yes	200 (63%)	226 (70%)	220 (70%)
No	120 (38%)	97 (30%)	95 (30%)
Comparison with Ranitidine 75mg [1]			0.996
Comparison with Placebo [1]		0.051	0.046

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

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Table 18.7 (Continued)
Summary of First Heartburn Episode Pain Relief Scores at 2 Hours

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	337	338	338
First Episode Rated Severe or Very Severe	320	323	315
Relief score of at least 4 (Considerate Relief)			
Yes	160 (50%)	182 (56%)	191 (61%)
No	160 (50%)	141 (44%)	124 (39%)
Comparison with Ranitidine 75mg [1]			0.239
Comparison with Placebo [1]		0.122	0.006
Relief Score of at least 5 (Almost Complete Relief)			
Yes	120 (38%)	155 (48%)	154 (49%)
No	200 (63%)	168 (52%)	161 (51%)
Comparison with Ranitidine 75mg [1]			0.783
Comparison with Placebo [1]		0.009	0.003
Relief Score of at least 6 (Complete Relief)			
Yes	83 (26%)	114 (35%)	113 (36%)
No	237 (74%)	209 (65%)	202 (64%)
Comparison with Ranitidine 75mg [1]			0.871
Comparison with Placebo [1]		0.012	0.007

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

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Table 10 Summary of Change in AGIDA Scores for Severe Heartburn --- RAN3013

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Table 25
Summary of Change in AGIDA Scores[1] for Severe Heartburn

	Placebo			Ranitidine 75mg			Ranitidine 150mg			P-values [2]		
Number of Subjects	337			338			338					
Subjs w/Total AGIDA Scores	325	311	302	323	317	303	328	310	303			
	Pre	Post	Change	Pre	Post	Change	Pre	Post	Change	Ran 150 v Ran 75	Ran 75 v Pbo	Ran 150 v Pbo
Heartburn	8.2	7.4	-0.8(0.1)	8.1	7.3	-0.8(0.1)	8.1	7.1	-0.9(0.1)	0.392	0.780	0.259
Acid/sour Taste	6.0	5.1	-0.9(0.1)	5.9	5.1	-0.9(0.1)	5.7	4.9	-0.9(0.1)	0.887	0.912	0.802
Sour Stomach	4.7	4.2	-0.6(0.2)	4.9	4.0	-0.9(0.1)	4.6	4.1	-0.6(0.1)	0.231	0.138	0.772
Stomach Ache	3.5	3.2	-0.4(0.2)	3.4	3.0	-0.4(0.1)	3.3	3.0	-0.3(0.1)	0.505	0.916	0.575
Upset Stomach	3.7	3.3	-0.4(0.1)	3.7	3.2	-0.5(0.1)	3.4	3.1	-0.3(0.2)	0.301	0.451	0.779
Nausea	2.3	2.2	-0.1(0.1)	2.5	2.2	-0.4(0.1)	2.4	2.1	-0.4(0.1)	0.811	0.170	0.261
Stomach Fullness/Bloating	4.8	4.7	-0.2(0.1)	4.6	4.3	-0.3(0.2)	4.6	4.4	-0.2(0.2)	0.721	0.552	0.814
Belching	5.6	5.0	-0.6(0.1)	5.5	4.8	-0.6(0.1)	5.3	4.6	-0.7(0.1)	0.733	0.742	0.505
Feeling Gassy Inside	5.7	5.3	-0.5(0.1)	5.4	4.9	-0.5(0.1)	5.5	4.8	-0.9(0.1)	0.034	0.954	0.040
Passing Gas	5.3	5.0	-0.3(0.1)	5.0	4.4	-0.5(0.1)	5.0	4.4	-0.6(0.1)	0.596	0.150	0.050
Total AGIDA Score[3]	49.8	45.5	-4.8(0.9)	49.2	43.0	-6.0(0.9)	47.5	42.0	-6.2(0.9)	0.938	0.342	0.304

[1] AGIDA = Abdominal-Gastric Index of Digestive Annoyances.
Change = Score at end of treatment (Post) - Score at end of Run-in (Pre).
[2] P-values were calculated using contrasts from analysis of variance with investigator in the model.
[3] All ten AGIDA items must be non-missing for determination of total AGIDA score.

ROTC$DATA:[PROTOCOLS.RANA3013.TABLES] EFFI_T11.SAS 09DEC98 12:16

Table 11 Summary of Non-Study Drug-Treated Heartburn Episodes --- RAN3013

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Table 29
Summary of Non-Study Drug-Treated Heartburn Episodes[1]

	1st 7 days of Run-in	1st 7 days of Treatment Phase	2nd 7 days of Treatment Phase	P-value for [1] change over time	P-value vs [2] Ran 75mg	P-value [2] vs Placebo
Placebo						
Subjects (w/ episodes)	337 (120)	(239)	(232)	<0.001		
Episodes						
N	471	1277	1352			
Mean(SE)	1.4(0.16)	3.8(0.24)	4.0(0.28)			
Median	0.0	2.0	2.0			
Min - Max	0 - 20	0 - 27	0 - 29			
Ranitidine 75mg						
Subjects (w/ episodes)	338 (114)	(224)	(217)	<0.001		0.490
Episodes						
N	515	1303	1287			
Mean(SE)	1.5(0.18)	3.9(0.26)	3.8(0.27)			
Median	0.0	2.0	3.0			
Min - Max	0 - 22	0 - 27	0 - 29			
Ranitidine 150mg						
Subjects (w/ episodes)	338 (123)	(249)	(236)	<0.001	0.192	0.049
Episodes						
N	598	1545	1608			
Mean(SE)	1.8(0.22)	4.6(0.38)	4.8(0.38)			
Median	0.0	3.0	3.0			
Min - Max	0 - 40	0 - 71	0 - 72			

[1] P-value testing the general hypothesis of no change in means over time was calculated from repeated measures ANOVA.
[2] P-value was computed using Generalized Estimating Equations with investigator in the model.
ROTC$DATA:[PROTOCOLS.RANA3013.TABLES] EFF_T161.SAS 09DEC98 14:38

Table 12 Summary of Relief of Nighttime Heartburn Affecting Sleep During Treatment Phase --- RAN3013

APPEARS THIS WAY
ON ORIGINAL

Table 31
Summary of Relief of Nighttime Heartburn Affecting Sleep During Treatment Phase

Number (%) of Nights

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	337	338	338
Heartburn Prevented Subject from Falling Asleep Previous Night			
Yes	561 (12%)	522 (11%)	490 (10%)
No	4014 (88%)	4108 (89%)	4260 (90%)
Comparison with Ranitidine 75mg [1]			0.552
Comparison with Placebo [1]		0.352	0.148
Heartburn Woke Subject During Previous Night			
Yes	725 (16%)	721 (16%)	610 (13%)
No	3811 (84%)	3907 (84%)	4134 (87%)
Comparison with Ranitidine 75mg [1]			0.174
Comparison with Placebo [1]		0.729	0.071
Subject Suffered from Either of the Above Conditions			
Yes	1050 (23%)	997 (22%)	894 (19%)
No	3481 (77%)	3621 (78%)	3841 (81%)
Comparison with Ranitidine 75mg [1]			0.239
Comparison with Placebo [1]		0.381	0.040

[1] P-values were calculated using Generalized Estimating Equations, adjusting for investigator.

ROTC$DATA:[PROTOCOLS.RANA3013.TABLES] EFFI_T17.SAS 09DEC98 12:05

Table 13 Baseline Patient Characteristic by Treatment Group --- Protocol RANA3014
All Randomized

Characteristic	Ranitidine 75 mg (N=334)	Ranitidine 150 mg (N=339)	Placebo (N=334)	Among Groups p-value
Gender				0.850
Male	179 (54%)	181 (53%)	185 (55%)	
Female	155 (46%)	158 (47%)	149 (45%)	
Race				0.899
Caucasian	271 (81%)	284 (84%)	278 (83%)	
Black	51 (15%)	44 (13%)	47 (13%)	
Hispanic	10 (3%)	9 (3%)	8 (2%)	
Oriental	1 (<1%)	0	0	
Other	1 (<1%)	2 (<1%)	1 (<1%)	
Age (yr)				0.143
Mean (SD)	43.4 (12.4)	41.6 (12.1)	42.5 (11.4)	
Height (inches)				0.821
Mean (SD)	67.5 (4.0)	67.6 (3.9)	67.7 (3.8)	
Weight (lbs)				0.549
N	334	339	331	
Mean (SD)	196.5 (43.3)	195.5 (44.7)	194.5 (45.5)	
Tobacco Use				0.283
No	237 (71%)	223 (66%)	235 (70%)	
Yes	97 (29%)	116 (34%)	99 (30%)	
Length of time (yrs) with heartburn, acid indigestion or sour stomach				0.385
Mean (SD)	10.3 (10.1)	10.1 (9.2)	10.9 (9.9)	
Did you ever see a doctor because of your heartburn, sour stomach or acid indigestion				0.013
No	166 (50%)	160 (47%)	194 (58%)	
Yes	168 (50%)	179 (53%)	140 (42%)	
How many days did you experience heartburn over the last week?				0.011
Mean (SD)	6.2 (1.1)	6.3 (1.1)	6.1 (1.1)	

Copied from Tables 7, 10 and 11.
P-value was calculated using Kruskal-Wallis test for continuous data.
P-value was calculated using Cochran-Mantel-Haenszel test for categorical data.

Table 13 Baseline Patient Characteristic by Treatment Group --- Protocol RANA3014
(Continued)

All Randomized

Characteristic	Ranitidine 75 mg (N=334)	Ranitidine 150 mg (N=339)	Placebo (N=334)	Among Groups p-value
How many days did you experience heartburn over the week before?				0.012
Mean (SD)	6.3 (1.1)	6.3 (0.9)	6.1 (1.1)	
On a typical day how many episodes of heartburn do you have?				0.442
Mean (SD)	2.7 (1.8)	2.6 (1.3)	2.5 (1.5)	
Describe most of your heartburn episodes over the last two weeks				0.317
Very mild	0	0	0	
Mild	0	0	0	
Moderate	1 (<1%)	0	0	
Severe	275 (82%)	269 (79%)	279 (84%)	
Very severe	58 (17%)	70 (21%)	55 (16%)	
What do you usually take for heartburn?				
Antacids	251 (75%)	252 (74%)	264 (79%)	0.311
OTC H2's	157 (47%)	136 (40%)	131 (39%)	0.083
Prescription H2's	48 (14%)	40 (12%)	34 (10%)	0.246
Pepto Bismol	10 (3%)	15 (4%)	11 (3%)	0.573
Other	21 (6%)	34 (10%)	25 (7%)	0.186
Frequency of heartburn medication				0.786
not every day	97 (29%)	103 (30%)	104 (31%)	
Daily – once per day	74 (22%)	63 (19%)	71 (21%)	
Daily – more than once per day	157 (47%)	163 (48%)	150 (45%)	

Copied from Tables 11and 12.
P-value was calculated using Kruskal-Wallis test for continuous data.
P-value was calculated using Cochran-Mantel-Haenszel test for categorical data.

Table 14 Summary of First Heartburn Episode Pain Relief Scores at 15 Minutes --- RAN3014

APPEARS THIS WAY
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Table 18
Summary of First Heartburn Episode Pain Relief Scores at 15 Minutes

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	334	334	339
First Episode Rated Severe or Very Severe	318	315	324
Relief Score of at least 1 (Little Relief)			
Yes	123 (39%)	127 (40%)	121 (37%)
No	195 (61%)	188 (60%)	203 (63%)
Comparison with Ranitidine 75mg [1]			0.523
Comparison with Placebo [1]		0.725	0.696
Relief Score of at least 2 (Some Relief)			
Yes	63 (20%)	66 (21%)	63 (19%)
No	255 (80%)	249 (79%)	261 (81%)
Comparison with Ranitidine 75mg [1]			0.708
Comparison with Placebo [1]		0.792	0.830
Relief Score of at least 3 (Moderate Relief)			
Yes	34 (11%)	28 (9%)	36 (11%)
No	284 (89%)	287 (91%)	288 (89%)
Comparison with Ranitidine 75mg [1]			0.328
Comparison with Placebo [1]		0.414	0.904

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

ROTC$DATA:[PROTOCOLS.RANA3014.TABLES] EFFI_T02.SAS 11DEC98 08:55

Table 18 (Continued)
Summary of First Heartburn Episode Pain Relief Scores at 15 Minutes

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	334	334	339
First Episode Rated Severe or Very Severe	318	315	324
Relief score of at least 4 (Considerate Relief)			
Yes	15 (5%)	12 (4%)	18 (6%)
No	303 (95%)	303 (96%)	306 (94%)
Comparison with Ranitidine 75mg [1]			0.306
Comparison with Placebo [1]		0.544	0.603
Relief Score of at least 5 (Almost Complete Relief)			
Yes	6 (2%)	6 (2%)	9 (3%)
No	312 (98%)	309 (98%)	315 (97%)
Comparison with Ranitidine 75mg [1]			0.398
Comparison with Placebo [1]		0.952	0.436
Relief Score of at least 6 (Complete Relief)			
Yes	3 (<1%)	0	4 (1%)
No	315(>99%)	315(100%)	320 (99%)
Comparison with Ranitidine 75mg [1]			0.044
Comparison with Placebo [1]		0.087	0.711

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

ROTC$DATA:[PROTOCOLS.RANA3014.TABLES] EFFI_T02.SAS 11DEC98 08:55

Table 15 Summary of First Heartburn Episode Pain Relief Scores at 30 Minutes --- RAN3014

APPEARS THIS WAY
ON ORIGINAL

Table 18.1
Summary of First Heartburn Episode Pain Relief Scores at 30 Minutes

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	334	334	339
First Episode Rated Severe or Very Severe	318	315	324
Relief Score of at least 1 (Little Relief)			
Yes	190 (60%)	188 (60%)	186 (57%)
No	128 (40%)	127 (40%)	138 (43%)
Comparison with Ranitidine 75mg [1]			0.623
Comparison with Placebo [1]		0.970	0.600
Relief Score of at least 2 (Some Relief)			
Yes	103 (32%)	112 (36%)	111 (34%)
No	215 (68%)	203 (64%)	213 (66%)
Comparison with Ranitidine 75mg [1]			0.854
Comparison with Placebo [1]		0.437	0.660
Relief Score of at least 3 (Moderate Relief)			
Yes	64 (20%)	63 (20%)	59 (18%)
No	254 (80%)	252 (80%)	265 (82%)
Comparison with Ranitidine 75mg [1]			0.632
Comparison with Placebo [1]		0.905	0.470

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

ROTC$DATA:[PROTOCOLS.RANA3014.TABLES] EFFI_T02.SAS 11DEC98 08:55

Table 18.1 (Continued)
Summary of First Heartburn Episode Pain Relief Scores at 30 Minutes

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	334	334	339
First Episode Rated Severe or Very Severe	318	315	324
Relief score of at least 4 (Considerate Relief)			
Yes	41 (13%)	30 (10%)	36 (11%)
No	277 (87%)	285 (90%)	288 (89%)
Comparison with Ranitidine 75mg [1]			0.489
Comparison with Placebo [1]		0.150	0.449
Relief Score of at least 5 (Almost Complete Relief)			
Yes	13 (4%)	12 (4%)	20 (6%)
No	305 (96%)	303 (96%)	304 (94%)
Comparison with Ranitidine 75mg [1]			0.162
Comparison with Placebo [1]		0.806	0.239
Relief Score of at least 6 (Complete Relief)			
Yes	8 (3%)	6 (2%)	8 (2%)
No	310 (97%)	309 (98%)	316 (98%)
Comparison with Ranitidine 75mg [1]			0.629
Comparison with Placebo [1]		0.598	0.958

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

Table 16 Summary of First Heartburn Episode Pain Relief Scores at 45 Minutes --- RAN3014

APPEARS THIS WAY
ON ORIGINAL

Table 18.2
Summary of First Heartburn Episode Pain Relief Scores at 45 Minutes

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	334	334	339
First Episode Rated Severe or Very Severe	318	315	324
Relief Score of at least 1 (Little Relief)			
Yes	239 (75%)	250 (79%)	258 (80%)
No	79 (25%)	65 (21%)	66 (20%)
Comparison with Ranitidine 75mg [1]			0.887
Comparison with Placebo [1]		0.194	0.175
Relief Score of at least 2 (Some Relief)			
Yes	155 (49%)	171 (54%)	167 (52%)
No	163 (51%)	144 (46%)	157 (48%)
Comparison with Ranitidine 75mg [1]			0.553
Comparison with Placebo [1]		0.174	0.489
Relief Score of at least 3 (Moderate Relief)			
Yes	95 (30%)	108 (34%)	117 (36%)
No	223 (70%)	207 (66%)	207 (64%)
Comparison with Ranitidine 75mg [1]			0.548
Comparison with Placebo [1]		0.239	0.104

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

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Table 18.2 (Continued)
Summary of First Heartburn Episode Pain Relief Scores at 45 Minutes

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	334	334	339
First Episode Rated Severe or Very Severe	318	315	324
Relief score of at least 4 (Considerate Relief)			
Yes	59 (19%)	59 (19%)	60 (19%)
No	259 (81%)	256 (81%)	264 (81%)
Comparison with Ranitidine 75mg [1]			0.996
Comparison with Placebo [1]		0.994	0.906
Relief Score of at least 5 (Almost Complete Relief)			
Yes	28 (9%)	31 (10%)	40 (12%)
No	290 (91%)	284 (90%)	284 (88%)
Comparison with Ranitidine 75mg [1]			0.287
Comparison with Placebo [1]		0.692	0.153
Relief Score of at least 6 (Complete Relief)			
Yes	18 (6%)	16 (5%)	18 (6%)
No	300 (94%)	299 (95%)	306 (94%)
Comparison with Ranitidine 75mg [1]			0.762
Comparison with Placebo [1]		0.687	0.921

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

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Table 17 Summary of First Heartburn Episode Pain Relief Scores at 1 Hour --- RAN3014

APPEARS THIS WAY
ON ORIGINAL

Table 18.3
Summary of First Heartburn Episode Pain Relief Scores at 1 Hour

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	334	334	339
First Episode Rated Severe or Very Severe	318	315	324
Relief Score of at least 1 (Little Relief)			
Yes	268 (84%)	270 (86%)	289 (89%)
No	50 (16%)	45 (14%)	35 (11%)
Comparison with Ranitidine 75mg [1]			0.162
Comparison with Placebo [1]		0.549	0.069
Relief Score of at least 2 (Some Relief)			
Yes	204 (64%)	213 (68%)	220 (68%)
No	114 (36%)	102 (32%)	104 (32%)
Comparison with Ranitidine 75mg [1]			0.895
Comparison with Placebo [1]		0.303	0.322
Relief Score of at least 3 (Moderate Relief)			
Yes	133 (42%)	152 (48%)	152 (47%)
No	185 (58%)	163 (52%)	172 (53%)
Comparison with Ranitidine 75mg [1]			0.854
Comparison with Placebo [1]		0.096	0.186

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

ROTC$DATA:[PROTOCOLS.RANA3014.TABLES] EFFI_T02.SAS 11DEC98 08:55

Table 18.3 (Continued)
Summary of First Heartburn Episode Pain Relief Scores at 1 Hour

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	334	334	339
First Episode Rated Severe or Very Severe	318	315	324
Relief score of at least 4 (Considerate Relief)			
Yes	88 (28%)	100 (32%)	98 (30%)
No	230 (72%)	215 (68%)	226 (70%)
Comparison with Ranitidine 75mg [1]			0.756
Comparison with Placebo [1]		0.264	0.518
Relief Score of at least 5 (Almost Complete Relief)			
Yes	55 (17%)	58 (18%)	69 (21%)
No	263 (83%)	257 (82%)	255 (79%)
Comparison with Ranitidine 75mg [1]			0.322
Comparison with Placebo [1]		0.738	0.217
Relief Score of at least 6 (Complete Relief)			
Yes	34 (11%)	36 (11%)	39 (12%)
No	284 (89%)	279 (89%)	285 (88%)
Comparison with Ranitidine 75mg [1]			0.777
Comparison with Placebo [1]		0.787	0.631

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

ROTC$DATA:[PROTOCOLS.RANA3014.TABLES] EFFI_T02.SAS 11DEC98 08:55

Table 18 Summary of First Heartburn Episode Pain Relief Scores at 1 Hour 15 Minutes -- - RAN3014

APPEARS THIS WAY
ON ORIGINAL

Table 18.4
Summary of First Heartburn Episode Pain Relief Scores at 1 Hour 15 Minutes

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	334	334	339
First Episode Rated Severe or Very Severe	318	315	324
Relief Score of at least 1 (Little Relief)			
Yes	270 (85%)	277 (88%)	302 (93%)
No	48 (15%)	38 (12%)	22 (7%)
Comparison with Ranitidine 75mg [1]			0.020
Comparison with Placebo [1]		0.223	<0.001
Relief Score of at least 2 (Some Relief)			
Yes	219 (69%)	233 (74%)	250 (77%)
No	99 (31%)	82 (26%)	74 (23%)
Comparison with Ranitidine 75mg [1]			0.312
Comparison with Placebo [1]		0.136	0.018
Relief Score of at least 3 (Moderate Relief)			
Yes	171 (54%)	188 (60%)	189 (58%)
No	147 (46%)	127 (40%)	135 (42%)
Comparison with Ranitidine 75mg [1]			0.779
Comparison with Placebo [1]		0.139	0.263

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

ROTC$DATA:[PROTOCOLS.RANA3014.TABLES] EFFI_T02.SAS 11DEC98 08:55

Table 18.4 (Continued)
Summary of First Heartburn Episode Pain Relief Scores at 1 Hour 15 Minutes

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	334	334	339
First Episode Rated Severe or Very Severe	318	315	324
Relief score of at least 4 (Considerate Relief)			
Yes	118 (37%)	127 (40%)	133 (41%)
No	200 (63%)	188 (60%)	191 (59%)
Comparison with Ranitidine 75mg [1]			0.796
Comparison with Placebo [1]		0.405	0.335
Relief Score of at least 5 (Almost Complete Relief)			
Yes	76 (24%)	82 (26%)	92 (28%)
No	242 (76%)	233 (74%)	232 (72%)
Comparison with Ranitidine 75mg [1]			0.433
Comparison with Placebo [1]		0.586	0.216
Relief Score of at least 6 (Complete Relief)			
Yes	48 (15%)	54 (17%)	61 (19%)
No	270 (85%)	261 (83%)	263 (81%)
Comparison with Ranitidine 75mg [1]			0.559
Comparison with Placebo [1]		0.532	0.232

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

ROTC$DATA:[PROTOCOLS.RANA3014.TABLES] EFFI_T02.SAS 11DEC98 08:55

Table 19 Summary of First Heartburn Episode Pain Relief Scores at 1 Hour 30 Minutes -- - RAN3014

APPEARS THIS WAY
ON ORIGINAL

Table 18.5
Summary of First Heartburn Episode Pain Relief Scores at 1 Hour 30 Minutes

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	334	334	339
First Episode Rated Severe or Very Severe	318	315	324
Relief Score of at least 1 (Little Relief)			
Yes	273 (86%)	285 (90%)	304 (94%)
No	45 (14%)	30 (10%)	20 (6%)
Comparison with Ranitidine 75mg [1]			0.117
Comparison with Placebo [1]		0.059	0.001
Relief Score of at least 2 (Some Relief)			
Yes	228 (72%)	244 (77%)	267 (82%)
No	90 (28%)	71 (23%)	57 (18%)
Comparison with Ranitidine 75mg [1]			0.105
Comparison with Placebo [1]		0.092	0.001
Relief Score of at least 3 (Moderate Relief)			
Yes	181 (57%)	204 (65%)	215 (66%)
No	137 (43%)	111 (35%)	109 (34%)
Comparison with Ranitidine 75mg [1]			0.618
Comparison with Placebo [1]		0.047	0.016

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

ROTC$DATA:[PROTOCOLS.RANA3014.TABLES] EFFI_T02.SAS 11DEC98 08:55

Table 18.5 (Continued)
Summary of First Heartburn Episode Pain Relief Scores at 1 Hour 30 Minutes

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	334	334	339
First Episode Rated Severe or Very Severe	318	315	324
Relief score of at least 4 (Considerate Relief)			
Yes	138 (43%)	154 (49%)	155 (48%)
No	180 (57%)	161 (51%)	169 (52%)
Comparison with Ranitidine 75mg [1]			0.829
Comparison with Placebo [1]		0.178	0.303
Relief Score of at least 5 (Almost Complete Relief)			
Yes	95 (30%)	104 (33%)	106 (33%)
No	223 (70%)	211 (67%)	218 (67%)
Comparison with Ranitidine 75mg [1]			0.980
Comparison with Placebo [1]		0.443	0.479
Relief Score of at least 6 (Complete Relief)			
Yes	64 (20%)	68 (22%)	72 (22%)
No	254 (80%)	247 (78%)	252 (78%)
Comparison with Ranitidine 75mg [1]			0.806
Comparison with Placebo [1]		0.732	0.562

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

ROTC$DATA:[PROTOCOLS.RANA3014.TABLES] EFFI_T02.SAS 11DEC98 08:55

Table 20 Summary of First Heartburn Episode Pain Relief Scores at 1 Hour 45 Minutes -- - RAN3014

APPEARS THIS WAY
ON ORIGINAL

Table 18.6
Summary of First Heartburn Episode Pain Relief Scores at 1 Hour 45 Minutes

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	334	334	339
First Episode Rated Severe or Very Severe	318	315	324
Relief Score of at least 1 (Little Relief)			
Yes	268 (84%)	287 (91%)	305 (94%)
No	50 (16%)	28 (9%)	19 (6%)
Comparison with Ranitidine 75mg [1]			0.152
Comparison with Placebo [1]		0.006	<0.001
Relief Score of at least 2 (Some Relief)			
Yes	229 (72%)	250 (79%)	276 (85%)
No	89 (28%)	65 (21%)	48 (15%)
Comparison with Ranitidine 75mg [1]			0.051
Comparison with Placebo [1]		0.029	<0.001
Relief Score of at least 3 (Moderate Relief)			
Yes	195 (61%)	217 (69%)	235 (73%)
No	123 (39%)	98 (31%)	89 (27%)
Comparison with Ranitidine 75mg [1]			0.272
Comparison with Placebo [1]		0.046	0.003

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

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Table 18.6 (Continued)
Summary of First Heartburn Episode Pain Relief Scores at 1 Hour 45 Minutes

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	334	334	339
First Episode Rated Severe or Very Severe	318	315	324
Relief score of at least 4 (Considerate Relief)			
Yes	154 (48%)	173 (55%)	184 (57%)
No	164 (52%)	142 (45%)	140 (43%)
Comparison with Ranitidine 75mg [1]			0.585
Comparison with Placebo [1]		0.108	0.040
Relief Score of at least 5 (Almost Complete Relief)			
Yes	106 (33%)	127 (40%)	126 (39%)
No	212 (67%)	188 (60%)	198 (61%)
Comparison with Ranitidine 75mg [1]			0.747
Comparison with Placebo [1]		0.077	0.161
Relief Score of at least 6 (Complete Relief)			
Yes	74 (23%)	82 (26%)	83 (26%)
No	244 (77%)	233 (74%)	241 (74%)
Comparison with Ranitidine 75mg [1]			0.941
Comparison with Placebo [1]		0.476	0.538

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

Table 21 Summary of First Heartburn Episode Pain Relief Scores at 2 Hours --- RAN3014

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Table 18.7
Summary of First Heartburn Episode Pain Relief Scores at 2 Hours

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	334	334	339
First Episode Rated Severe or Very Severe	318	315	324
Relief Score of at least 1 (Little Relief)			
Yes	269 (85%)	288 (91%)	305 (94%)
No	49 (15%)	27 (9%)	19 (6%)
Comparison with Ranitidine 75mg [1]			0.197
Comparison with Placebo [1]		0.006	<0.001
Relief Score of at least 2 (Some Relief)			
Yes	232 (73%)	256 (81%)	279 (86%)
No	86 (27%)	59 (19%)	45 (14%)
Comparison with Ranitidine 75mg [1]			0.096
Comparison with Placebo [1]		0.012	<0.001
Relief Score of at least 3 (Moderate Relief)			
Yes	199 (63%)	225 (71%)	241 (74%)
No	119 (37%)	90 (29%)	83 (26%)
Comparison with Ranitidine 75mg [1]			0.354
Comparison with Placebo [1]		0.018	0.001

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

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Table 18.7 (Continued)
Summary of First Heartburn Episode Pain Relief Scores at 2 Hours

Number (%) of Subjects

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	334	334	339
First Episode Rated Severe or Very Severe	318	315	324
Relief score of at least 4 (Considerate Relief)			
Yes	162 (51%)	193 (61%)	197 (61%)
No	156 (49%)	122 (39%)	127 (39%)
Comparison with Ranitidine 75mg [1]			0.984
Comparison with Placebo [1]		0.009	0.014
Relief Score of at least 5 (Almost Complete Relief)			
Yes	121 (38%)	144 (46%)	151 (47%)
No	197 (62%)	171 (54%)	173 (53%)
Comparison with Ranitidine 75mg [1]			0.775
Comparison with Placebo [1]		0.057	0.036
Relief Score of at least 6 (Complete Relief)			
Yes	86 (27%)	106 (34%)	103 (32%)
No	232 (73%)	209 (66%)	221 (68%)
Comparison with Ranitidine 75mg [1]			0.623
Comparison with Placebo [1]		0.082	0.221

[1] P-values were calculated using Cochran-Mantel-Haenszel test stratified by investigator.
Includes first episodes that were rated as severe or very severe.

Table 22 Summary of Change in AGIDA Scores for Severe Heartburn --- RAN3014

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Table 25
Summary of Change in AGIDA Scores[1] for Severe Heartburn

	Placebo			Ranitidine 75mg			Ranitidine 150mg			P-values [2]		
Number of Subjects	334			334			339					
Subjs w/Total AGIDA Scores	314	308	293	317	314	298	323	319	304			
	Pre	Post	Change	Pre	Post	Change	Pre	Post	Change	Ran 150 v Ran 75	Ran 75 v Pbo	Ran 150 v Pbo
Heartburn	7.7	7.1	-0.6(0.1)	8.0	6.9	-1.1(0.1)	8.1	6.9	-1.2(0.1)	0.657	0.005	0.001
Acid/sour Taste	5.7	5.1	-0.7(0.1)	5.6	4.6	-1.1(0.1)	5.5	4.7	-0.8(0.2)	0.132	0.049	0.631
Sour Stomach	4.4	4.0	-0.4(0.1)	4.5	3.6	-1.0(0.1)	4.4	3.8	-0.7(0.2)	0.155	0.002	0.101
Stomach Ache	2.9	2.7	-0.3(0.1)	3.3	2.6	-0.7(0.1)	3.1	2.8	-0.3(0.2)	0.055	0.023	0.714
Upset Stomach	3.2	3.0	-0.2(0.1)	3.3	2.7	-0.6(0.1)	3.2	2.8	-0.4(0.1)	0.524	0.090	0.286
Nausea	2.1	1.9	-0.2(0.1)	2.4	1.9	-0.5(0.1)	2.2	2.2	0.0(0.1)	0.019	0.166	0.346
Stomach Fullness/Bloating	4.2	4.1	-0.1(0.1)	4.5	4.1	-0.4(0.1)	4.3	3.9	-0.5(0.2)	0.415	0.210	0.039
Belching	4.9	4.5	-0.5(0.1)	5.0	4.3	-0.8(0.2)	5.0	4.3	-0.8(0.1)	0.636	0.136	0.306
Feeling Gassy Inside	5.0	4.4	-0.6(0.1)	5.0	4.3	-0.7(0.2)	5.2	4.4	-0.8(0.1)	0.567	0.607	0.278
Passing Gas	4.5	4.1	-0.4(0.1)	4.6	4.1	-0.5(0.1)	5.0	4.3	-0.8(0.1)	0.194	0.457	0.041
Total AGIDA Score[3]	44.1	40.8	-4.0(0.8)	45.9	39.1	-7.4(0.9)	45.8	40.2	-6.2(0.9)	0.319	0.005	0.069

[1] AGIDA = Abdominal-Gastric Index of Digestive Annoyances.
Change = Score at end of treatment (Post) - Score at end of Run-in (Pre).
[2] P-values were calculated using contrasts from analysis of variance with investigator in the model.
[3] All ten AGIDA items must be non-missing for determination of total AGIDA score.

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Table 23 Summary of Non-Study Drug-Treated Heartburn Episodes --- RAN3014

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Table 29
Summary of Non-Study Drug-Treated Heartburn Episodes[1]

	1st 7 days of Run-in	1st 7 days of Treatment Phase	2nd 7 days of Treatment Phase	P-value for [1] change over time	P-value vs [2] Ran 75mg	P-value [2] vs Placebo
Placebo						
Subjects (w/ episodes)	334 (124)	(204)	(199)	<0.001		
Episodes						
N	446	1098	1149			
Mean(SE)	1.3(0.16)	3.3(0.23)	3.4(0.27)			
Median	0.0	2.0	2.0			
Min - Max	0 - 18	0 - 22	0 - 35			
Ranitidine 75mg						
Subjects (w/ episodes)	334 (144)	(227)	(212)	<0.001		0.767
Episodes						
N	533	1148	1185			
Mean(SE)	1.6(0.16)	3.4(0.22)	3.5(0.28)			
Median	0.0	2.0	2.0			
Min - Max	0 - 17	0 - 24	0 - 39			
Ranitidine 150mg						
Subjects (w/ episodes)	339 (123)	(224)	(214)	<0.001	0.325	0.566
Episodes						
N	560	1171	1204			
Mean(SE)	1.7(0.19)	3.5(0.24)	3.6(0.25)			
Median	0.0	2.0	2.0			
Min - Max	0 - 29	0 - 26	0 - 26			

[1] P-value testing the general hypothesis of no change in means over time was calculated from repeated measures ANOVA.
[2] P-value was computed using Generalized Estimating Equations with investigator in the model.
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Table 24 Summary of Relief of Nighttime Heartburn Affecting Sleep During Treatment Phase --- RAN3014

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Table 31
Summary of Relief of Nighttime Heartburn Affecting Sleep During Treatment Phase

Number (%) of Nights

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	334	334	339
Heartburn Prevented Subject from Falling Asleep Previous Night			
Yes	433 (9%)	501 (11%)	500 (10%)
No	4264 (91%)	4240 (89%)	4280 (90%)
Comparison with Ranitidine 75mg [1]			0.851
Comparison with Placebo [1]		0.474	0.326
Heartburn Woke Subject During Previous Night			
Yes	695 (15%)	663 (14%)	705 (15%)
No	3995 (85%)	4075 (86%)	4053 (85%)
Comparison with Ranitidine 75mg [1]			0.699
Comparison with Placebo [1]		0.656	0.989
Subject Suffered from Either of the Above Conditions			
Yes	944 (20%)	956 (20%)	1021 (21%)
No	3744 (80%)	3776 (80%)	3737 (79%)
Comparison with Ranitidine 75mg [1]			0.493
Comparison with Placebo [1]		0.923	0.507

[1] P-values were calculated using Generalized Estimating Equations, adjusting for investigator.

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